

BENZIMIDAZOLE DERIVATIVES, COMPOSITIONS CONTAINING THEM, PREPARATION THEREOF AND USES THEREOF

5 BACKGROUND OF THE INVENTION

1. Field of the invention

The invention is related to therapeutic compounds, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof. Particularly, the present invention is related to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and/or cardiovascular disorders.

2. Discussion of Relevant Technology

Pain management has been an important field of study for many years. It has been well known that cannabinoid receptor (e.g., CB₁ receptor, CB₂ receptor) ligands including agonists, antagonists and inverse agonists produce relief of pain in a variety of animal models by interacting with CB₁ and/or CB₂ receptors. Generally, CB₁ receptors are located predominately in the central nervous system, whereas CB₂ receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

While CB₁ receptor agonists, such as Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and anadamide, are useful in anti-nociception models in animals, they tend to exert undesired CNS side-effects, e.g., psychoactive side effects, the abuse potential, drug dependence and tolerance, etc. These undesired side effects are known to be mediated by the CB₁ receptors located in CNS. There are lines of evidence, however, suggesting that CB₁ agonists acting at peripheral sites or with limited CNS exposure can manage pain in humans or animals with much improved overall in vivo profile.

Therefore, there is a need for new CB₁ receptor ligands such as agonists that may be useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects.

DESCRIPTION OF THE EMBODIMENTS

The present invention provides CB₁ receptor ligands which may be useful in treating pain and/or other related symptoms or diseases.

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures.

"CB₁/CB₂ receptors" means CB₁ and/or CB₂ receptors.

10 The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

15 The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

20 The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms. Unless otherwise specified, "alkyl" general includes both saturated alkyl and unsaturated alkyl.

The term "alkylene" used alone or as a suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serves to links two structures together.

25 The term "alkenyl" used alone or as a suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms.

The term "alkynyl" used alone or as a suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.

30 The term "cycloalkyl," used alone or as a suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms. "Cycloalkyl" includes both monocyclic and multicyclic hydrocarbon

structures. Multicyclic hydrocarbon structure includes non-fused, fused and bridged rings.

The term "cycloalkenyl" used alone or as a suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms. "Cycloalkenyl" includes both monocyclic and multicyclic hydrocarbon structures. Multicyclic hydrocarbon structure includes non-fused, fused and bridged rings.

The term "cycloalkynyl" used alone or as a suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms.

The term "aryl" used alone or as a suffix or prefix, refers to a hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (e.g., $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms, wherein the radical is located on a carbon of the aromatic ring.

The term "non-aromatic group" or "non-aromatic" used alone, as a suffix or as prefix, refers to a chemical group or radical that does not contain a ring having aromatic character (e.g., $4n + 2$ delocalized electrons).

The term "arylene" used alone or as a suffix or prefix, refers to a divalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (e.g., $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms, which serves to link two structures together.

The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroalkyl" used alone or as a suffix or prefix, refers to a radical formed as a result of replacing one or more carbon atom of an alkyl with one or more heteroatoms selected from N, O, P and S.

The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-containing structure or molecule has an aromatic character (*e.g.*, $4n + 2$ delocalized electrons).

The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

10 The term "heterocyclyl" used alone or as a suffix or prefix, refers a radical derived from a heterocycle by removing at least one hydrogen from a carbon of a ring of the heterocycle.

The term "heterocyclylene" used alone or as a suffix or prefix, refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, 15 which serves to link two structures together.

The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character, wherein the radical of the heterocyclyl is located on a carbon of an aromatic ring of the heterocyclyl. A heteroaryl may contain both aromatic and non-aromatic rings therein. These rings may be fused or 20 otherwisely linked together.

The term "heterocycloalkyl" used alone or as a suffix or prefix, refers to a heterocyclyl that does not have aromatic character.

The term "heteroarylene" used alone or as a suffix or prefix, refers to a heterocyclylene having aromatic character.

25 The term "heterocycloalkylene" used alone or as a suffix or prefix, refers to a heterocyclylene that does not have aromatic character.

The term "six-membered" used as a prefix refers to a group having a ring that contains six ring atoms.

30 The term "five-membered" used as a prefix refers to a group having a ring that contains five ring atoms.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl.

5 A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "substituted" used as a prefix refers to a structure, molecule or
10 group, wherein one or more hydrogens are replaced with one or more C₁₋₁₂hydrocarbon groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups containing one or more heteroatoms include heterocyclyl, -NO₂, -OR, -Cl, -Br, -I, -F, -CF₃, -C(=O)R, -C(=O)OH, -NH₂, -SH, -NHR, -NR₂, -SR, -SO₃H, -SO₂R, -S(=O)R, -
15 CN, -OH, -C(=O)OR, -C(=O)NR₂, -NRC(=O)R, oxo (=O), imino (=NR), thio (=S), and oximino (=N-OR), wherein each "R" is a C₁₋₁₂hydrocarbyl. For example, substituted phenyl may refer to nitrophenyl, pyridylphenyl, methoxyphenyl, chlorophenyl, aminophenyl, etc., wherein the nitro, pyridyl, methoxy, chloro, and amino groups may replace any suitable hydrogen on the phenyl ring.

20 The term "substituted" used as a suffix of a first structure, molecule or group, followed by one or more names of chemical groups refers to a second structure, molecule or group, which is a result of replacing one or more hydrogens of the first structure, molecule or group with the one or more named chemical groups. For example, a "phenyl substituted by nitro" refers to nitrophenyl.

25 The term "optionally substituted" refers to both groups, structures, or molecules that are substituted and those that are not substituted.

Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-
30 dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane,

homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4-oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl,

tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolynyl, isoindolynyl, quinolynyl, tetrahydroquinolynyl, isoquinolynyl, tetrahydroisoquinolynyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizynyl, isoindolyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolynyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocyclyls include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula $-O-R$, wherein $-R$ is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

The term "aryloxy" used alone or as a suffix or prefix, refers to radicals of the general formula $-O-Ar$, wherein $-Ar$ is an aryl.

The term "heteroaryloxy" used alone or as a suffix or prefix, refers to radicals of the general formula $-O-Ar'$, wherein $-Ar'$ is a heteroaryl.

The term "amine" or "amino" used alone or as a suffix or prefix, refers to radicals of the general formula $-NRR'$, wherein R and R' are independently selected from hydrogen or a hydrocarbon radical.

"Acyl" used alone, as a prefix or suffix, means $-C(=O)-R$, wherein $-R$ is an optionally substituted hydrocarbyl, hydrogen, amino or alkoxy. Acyl groups include, for example, acetyl, propionyl, benzoyl, phenyl acetyl, carboethoxy, and dimethylcarbamoyl.

Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on the group is replaced with one or more halogens.

"RT" or "rt" means room temperature.

5 A first ring group being "fused" with a second ring group means the first ring and the second ring share at least two atoms therebetween.

"Link," "linked," or "linking," unless otherwise specified, means covalently linked or bonded.

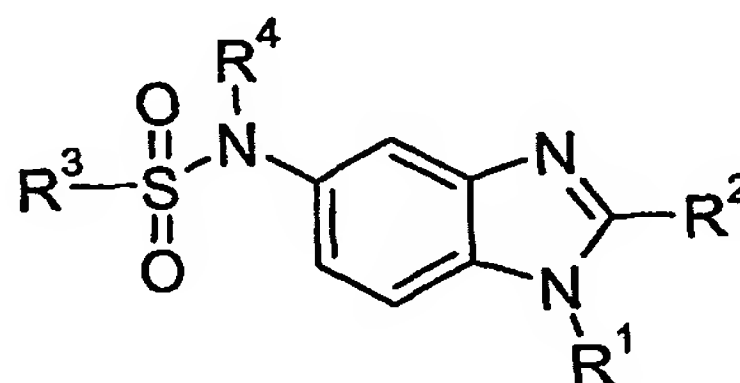
10 When a first group, structure, or atom is "directly connected" to a second group, structure or atom, at least one atom of the first group, structure or atom forms a chemical bond with at least one atom of the second group, structure or atom.

"Saturated carbon" means a carbon atom in a structure, molecule or group wherein all the bonds connected to this carbon atom are single bond. In other words, there is no double or triple bonds connected to this carbon atom and this carbon atom
15 generally adopts an sp^3 atomic orbital hybridization.

"Unsaturated carbon" means a carbon atom in a structure, molecule or group wherein at least one bond connected to this carbon atom is not a single bond. In other words, there is at least one double or triple bond connected to this carbon atom and this carbon atom generally adopts a sp or sp^2 atomic orbital hybridization.

20

In one aspect, an embodiment of the invention provides a compound of Formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

25

wherein

R^1 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $R^5R^6N-C_{1-6}$ alkyl, R^5O-C_{1-6} alkyl, $R^5C(=O)N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2-C_{1-6}$ alkyl, $R^5CS(=O)_2N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NC(=O)N(-R^7)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2N(R^7)-C_{1-6}$ alkyl, C_{6-10} aryl-
30 C_{1-6} alkyl, C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl-

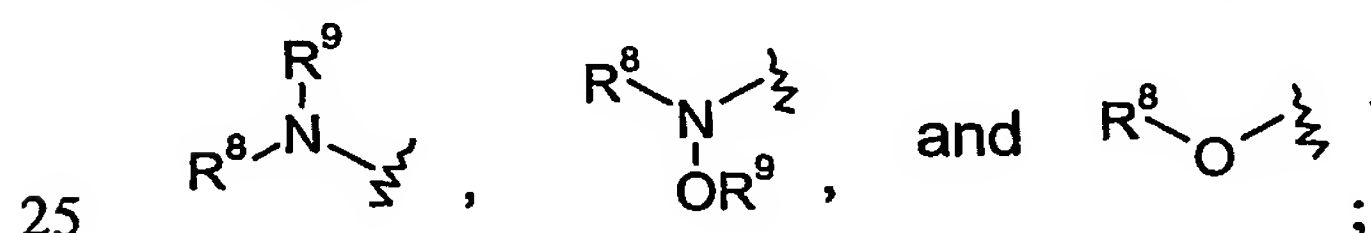
C₁₋₆alkyl, C₃₋₆heterocyclyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C(=O)-C₁₋₆alkyl,
 C₁₋₁₀hydrocarbylamino, R⁵R⁶N-, R⁵O-, R⁵C(=O)N(-R⁶)-, R⁵R⁶NS(=O)₂-,
 R⁵CS(=O)₂N(-R⁶)-, R⁵R⁶NC(=O)N(-R⁷)-, R⁵R⁶NS(=O)₂N(R⁷)-, C₆₋₁₀aryl, C₆₋₁₀aryl-
 C(=O)-, C₃₋₁₀cycloalkyl, C₄₋₈cycloalkenyl, C₃₋₆heterocyclyl and C₃₋₆heterocyclyl-

5 C(=O)-; wherein said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₆₋₁₀aryl-C₁₋₆alkyl,
 C₆₋₁₀aryl-C(=O)-C₁₋₆alkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl,
 C₃₋₆heterocyclyl-C₁₋₆alkyl, C₃₋₆heterocyclyl-C(=O)-C₁₋₆alkyl, C₁₋₁₀hydrocarbylamino,
 C₆₋₁₀aryl, C₆₋₁₀aryl-C(=O)-, C₃₋₁₀cycloalkyl, C₄₋₈cycloalkenyl, C₃₋₆heterocyclyl or
 C₃₋₆heterocyclyl-C(=O)- used in defining R¹ is optionally substituted by one or more
 10 groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy,
 and -NR⁵R⁶;

R² is selected from C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀
 cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl-C₁₋₆alkyl, C₄₋₈
 cycloalkenyl, R⁵R⁶N-, C₃₋₅heteroaryl, C₆₋₁₀aryl and C₃₋₆heterocycloalkyl, wherein
 15 said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl-C₁₋₆alkyl,
 C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl, C₃₋₅
 heteroaryl, C₆₋₁₀aryl or C₃₋₆heterocycloalkyl used in defining R² is optionally
 substituted by one or more groups selected from halogen, cyano, nitro, methoxy,
 ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶;

20 wherein R⁵, R⁶ and R⁷ are independently selected from -H, C₁₋₆alkyl, C₂₋₆
 alkenyl, C₂₋₆alkynyl, and a divalent C₁₋₆group that together with another divalent R⁵,
 R⁶ or R⁷ forms a portion of a ring;

R³ is selected from -H, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl,
 C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₄₋₈cycloalkenyl-C₁₋₆alkyl, C₃₋₆heterocycloalkyl,



optionally substituted with one or more groups selected from C₁₋₆alkyl, halogen,
 amino and C₁₋₆alkoxy;

each of R⁸ and R⁹ is independently selected from -H, C₁₋₁₀alkyl, C₂₋₁₀alkenyl,
 C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₃₋₆heterocyclyl, C₆₋₁₀aryl,
 30 C₃₋₆heterocyclyl-C₁₋₆alkyl, C₆₋₁₀aryl-C₁₋₆alkyl, and a divalent C₁₋₆group that together
 with another divalent group selected from R⁸ and R⁹ forms a portion of a ring,

wherein said C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, C₃₋₆heterocyclyl, C₆₋₁₀aryl, C₃₋₆heterocycl-C₁₋₆alkyl, C₆₋₁₀aryl-C₁₋₆alkyl, or divalent C₁₋₆group is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶; and

5 R⁴ is selected from -H, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₆alkyl, and C₄₋₈cycloalkenyl-C₁₋₆alkyl.

Another embodiment of the invention provides compounds of Formula I, wherein

10 R¹ is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, phenyl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl-C₁₋₄alkyl, C₄₋₆cycloalkenyl-C₁₋₄alkyl, C₃₋₆heterocycl-C₁₋₄alkyl, C₆₋₁₀aryl, C₃₋₁₀cycloalkyl, C₃₋₆heterocycl and C₄₋₆cycloalkenyl; wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, phenyl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl-C₁₋₄alkyl, C₄₋₆cycloalkenyl-C₁₋₄alkyl, C₆₋₁₀aryl, C₃₋₆heterocycl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, C₃₋₆heterocycl and C₄₋₆cycloalkenyl used in defining R¹ is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and -NR⁵R⁶;

R² is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl, C₄₋₆cycloalkenyl-C₁₋₄alkyl, C₃₋₆heterocycloalkyl-C₁₋₄alkyl, C₄₋₆cycloalkenyl, C₃₋₅heteroaryl, R⁵R⁶N-, and phenyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl, C₄₋₆cycloalkenyl-C₁₋₄alkyl, C₃₋₆heterocycloalkyl-C₁₋₄alkyl, C₄₋₆cycloalkenyl, C₃₋₅heteroaryl, R⁵R⁶N-, and phenyl used in defining R² is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and -NR⁵R⁶;

25 R³ is selected from -H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₃₋₆heterocycloalkyl,

$$\text{R}^8 \text{---} \text{N} \begin{array}{l} \text{R}^8 \\ \text{R}^9 \end{array} \quad \text{and} \quad \text{R}^8 \text{---} \text{O} \text{---} \begin{array}{l} \text{R}^8 \\ \text{R}^9 \end{array}$$
 optionally substituted with one or more groups selected from C₁₋₆alkyl and halogen;

each of R⁸ and R⁹ is independently selected from -H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₆alkyl, C₃₋₆heterocycl and C₃₋₆heterocycl-C₁₋₆alkyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₆alkyl, C₃₋₆heterocycl, C₃₋₆heterocycl-C₁₋₆alkyl, and a divalent C₁₋₆group that together

with another divalent group selected from R^8 and R^9 forms a portion of a ring,
 wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl- C_{1-6} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl, C_{3-6} heterocyclyl- C_{1-6} alkyl, or
 5 divalent C_{1-6} group are optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and $-NR^5R^6$; and
 R^4 , R^5 and R^6 are independently selected from $-H$ and C_{1-3} alkyl.

A further embodiment of the invention provides compounds of Formula I,
 10 wherein R^1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocylcoalkyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{3-6} heterocylcoalkyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl used in
 15 defining R^1 is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$;

R^2 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl- C_{1-4} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl- C_{1-4} alkyl used in defining R^2 is optionally substituted by one or more groups selected
 20 from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and $-NR^5R^6$;

R^3 is selected from C_{2-5} alkyl, C_{3-6} heterocycloalkyl,

$R^8-N(R^9)-$ and R^8-O- optionally substituted with one or more C_{1-6} alkyl;

wherein said C_{3-6} heterocycloalkyl contains at least one nitrogen ring atom and the radical of C_{3-6} heterocycloalkyl is located on the at least one nitrogen ring atom,
 25 and each of R^8 and R^9 is independently selected from $-H$, C_{1-6} alkyl, morpholinyl- C_{1-3} alkyl, pyrrolidinyl- C_{1-3} alkyl, and piperidinyl- C_{1-3} alkyl, wherein said C_{1-6} alkyl, morpholinyl- C_{1-3} alkyl, pyrrolidinyl- C_{1-3} alkyl, and piperidinyl- C_{1-3} alkyl are optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and $-NR^5R^6$; and

30 R^4 , R^5 and R^6 are independently selected from $-H$ and C_{1-3} alkyl.

A further embodiment of the invention provides compounds of Formula I, wherein

R^1 is selected from cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl, cyclohexylethyl, cyclopentylethyl, 4,4-difluorocyclohexylmethyl, tetrahydropyranylmethyl, tetrahydropyranylethyl, tetrahydrofuranylmethyl, 1-piperidinylethyl, N-methyl-2-piperidinylethyl;

R^2 is selected from t-butyl, n-butyl, 2-methyl-2-butyl, isopentyl, 2-methoxy-2-propyl, 2-hydroxyl-propyl, trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, 1-methyl-propyl, 1,1-dimethyl-propyl, 1,1-dimethyl-3-buten-1-yl, ethyl, and 2-propyl;

R^3 is C_{3-5} alkyl and $R^9-N \begin{smallmatrix} R^8 \\ \diagup \end{smallmatrix}$, wherein R^4 , R^8 and R^9 are selected from -H and C_{1-3} alkyl.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I. It will further be understood that the present invention encompasses tautomers of the compounds of the Formula I.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the Formula I.

Within the scope of the invention are also salts of the compounds of the Formula I. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for

example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a
5 carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

10 In one embodiment, the compound of Formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as
15 pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB₁ receptors. More particularly, the compounds of the invention exhibit activity as agonist of the CB₁ receptors and are useful in therapy, especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis,
20 migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other disease states in which dysfunction of CB₁ receptors is present or implicated. Furthermore, the compounds of the invention may be used to treat cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders,
25 gastrointestinal disorders and cardiovascular disorders.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

30 Compounds of the invention are useful in disease states where degeneration or dysfunction of cannabinoid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the

invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson's disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following myocardial infarction, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the Formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be construed accordingly. The term

"therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring
5 conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound
10 of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be oral,
15 intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

20 For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents,
25 flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in
30 suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is

dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of Formula I as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of Formula I for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such therapy.

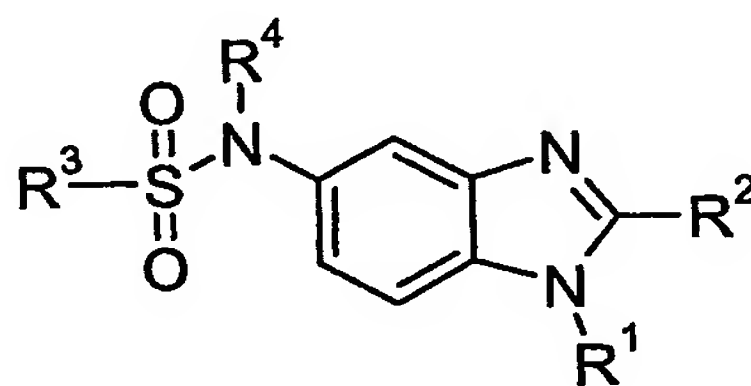
Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

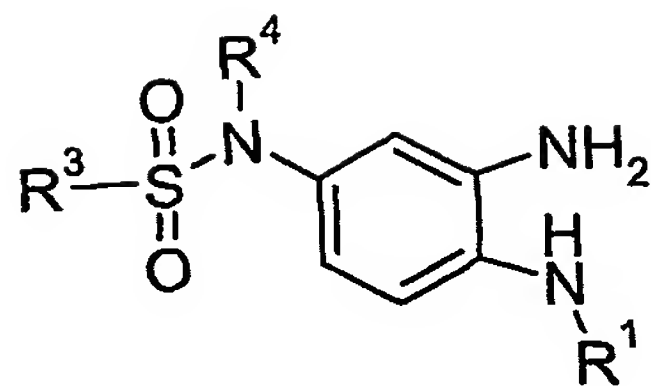
Another aspect of the invention is a method of preparing the compounds of the present invention.

In one embodiment, the method of the invention is a method for preparing a compound of Formula I,



I

comprising the step of reacting a compound of Formula II,



II

with a compound of R^2COX , in the presence of a base, such as an alkylamine, and optionally a coupling reagent, such as HATU, EDC, followed by treatment with an

5 acid such as AcOH,

wherein

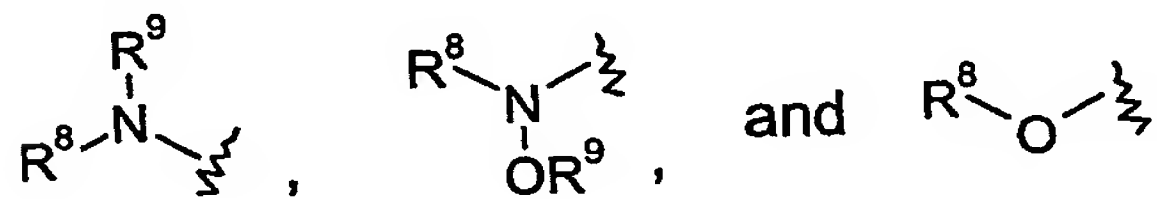
X is selected from Cl, Br, F and OH;

R^1 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $R^5R^6N-C_{1-6}$ alkyl, R^5O-C_{1-6} alkyl, $R^5C(=O)N(-R^6)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2-C_{1-6}$ alkyl, $R^5CS(=O)_2N(-R^6)-$
 10 C_{1-6} alkyl, $R^5R^6NC(=O)N(-R^7)-C_{1-6}$ alkyl, $R^5R^6NS(=O)_2N(R^7)-C_{1-6}$ alkyl, C_{6-10} aryl-
 C_{1-6} alkyl, C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl-
 C_{1-6} alkyl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-6}$ alkyl,
 C_{1-10} hydrocarbylamino, R^5R^6N- , R^5O- , $R^5C(=O)N(-R^6)-$, $R^5R^6NS(=O)_2-$,
 $R^5CS(=O)_2N(-R^6)-$, $R^5R^6NC(=O)N(-R^7)-$, $R^5R^6NS(=O)_2N(R^7)-$, C_{6-10} aryl, C_{6-10} aryl-
 15 $C(=O)-$, C_{3-10} cycloalkyl, C_{4-8} cycloalkenyl, C_{3-6} heterocyclyl and C_{3-6} heterocyclyl-
 $C(=O)-$; wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{6-10} aryl- C_{1-6} alkyl,
 C_{6-10} aryl- $C(=O)-C_{1-6}$ alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl,
 C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{3-6} heterocyclyl- $C(=O)-C_{1-6}$ alkyl, C_{1-10} hydrocarbylamino,
 C_{6-10} aryl, C_{6-10} aryl- $C(=O)-$, C_{3-10} cycloalkyl, C_{4-8} cycloalkenyl, C_{3-6} heterocyclyl or
 20 C_{3-6} heterocyclyl- $C(=O)-$ used in defining R^1 is optionally substituted by one or more
 groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy,
 and $-NR^5R^6$;

R^2 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl, R^5R^6N- , C_{3-5} heteroaryl, C_{6-10} aryl and C_{3-6} heterocycloalkyl, wherein
 25 said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-6} alkyl,
 C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl, C_{3-5} heteroaryl, C_{6-10} aryl or C_{3-6} heterocycloalkyl used in defining R^2 is optionally
 substituted by one or more groups selected from halogen, cyano, nitro, methoxy,
 30 ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$;

wherein R^5 , R^6 and R^7 are independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a divalent C_{1-6} group that together with another divalent R^5 , R^6 or R^7 forms a portion of a ring;

R^3 is selected from $-H$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{4-8} cycloalkenyl- C_{1-6} alkyl, C_{3-6} heterocycloalkyl,



optionally substituted with one or more

groups selected from C_{1-6} alkyl, halogen, amino and C_{1-6} alkoxy;

each of R^8 and R^9 is independently selected from $-H$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl, C_{6-10} aryl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{6-10} aryl- C_{1-6} alkyl, and a divalent C_{1-6} group that together with another divalent group selected from R^8 and R^9 forms a portion of a ring, wherein said C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, C_{3-6} heterocyclyl, C_{6-10} aryl, C_{3-6} heterocyclyl- C_{1-6} alkyl, C_{6-10} aryl- C_{1-6} alkyl, or divalent C_{1-6} group is optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$; and R^4 is selected from $-H$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, and C_{4-8} cycloalkenyl- C_{1-6} alkyl.

Particularly, the method of the invention is a method of preparing a compound of Formula I, wherein

X is selected from Cl , Br , F and OH ;

R^1 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, phenyl- C_{1-4} alkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{4-6} cycloalkenyl- C_{1-4} alkyl, C_{6-10} aryl, C_{3-6} heterocyclyl- C_{1-4} alkyl, C_{3-10} cycloalkyl, and C_{4-6} cycloalkenyl used in defining R^1 is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy, and $-NR^5R^6$;

R^2 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl- C_{1-4} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl-

C₁₋₄alkyl used in defining R² is optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and -NR⁵R⁶;

R³ is selected from -H, C₂₋₅alkyl, C₃₋₆heterocycloalkyl,

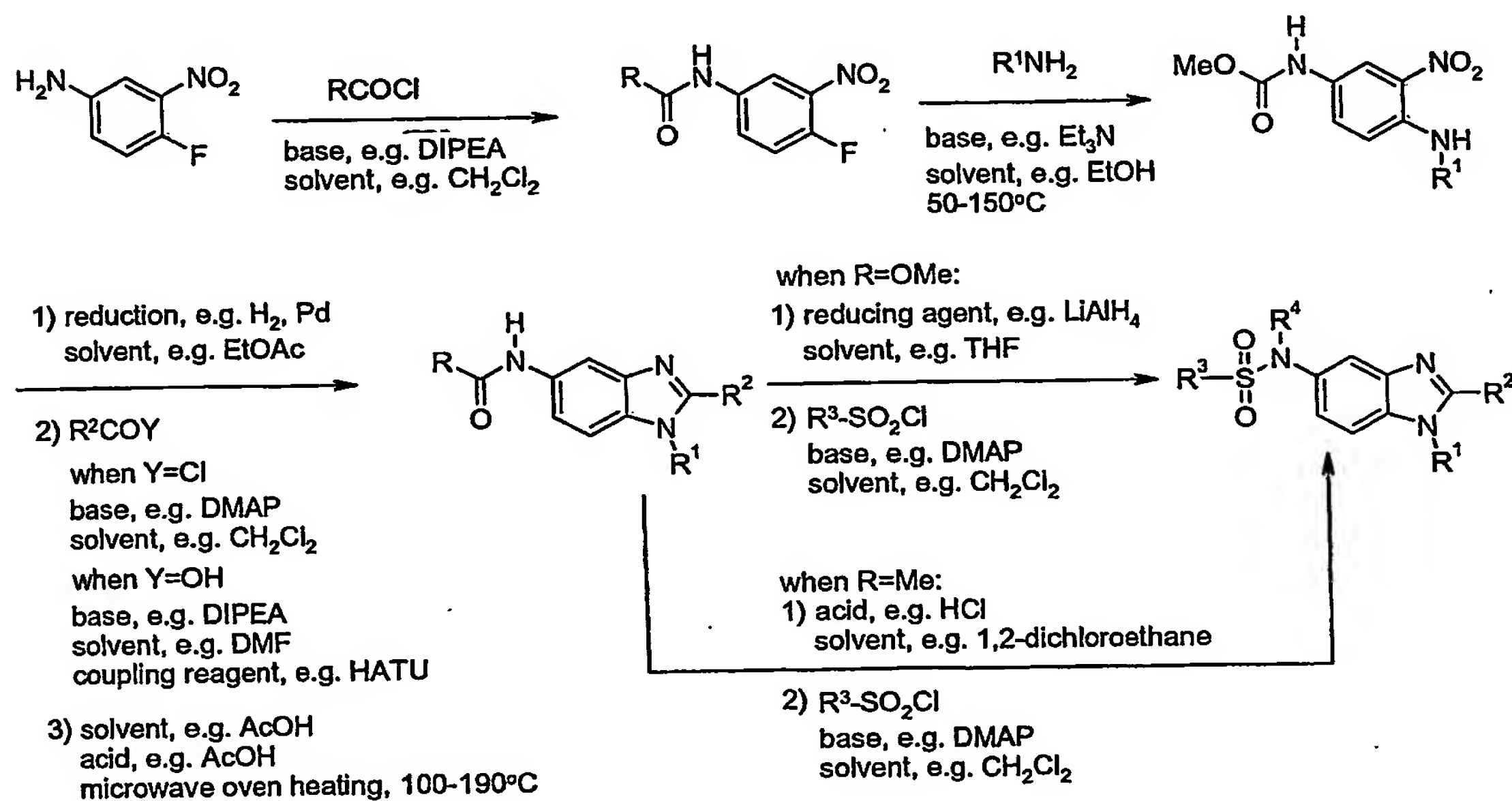
$\text{R}^9-\text{N}^{\text{R}^8}$ and $\text{R}^8-\text{O}-\text{Z}$ optionally substituted with one or more C₁₋₆alkyl;

- 5 wherein said C₃₋₆heterocycloalkyl contains at least one nitrogen ring atom and the radical of C₃₋₆heterocycloalkyl is located on the at least one nitrogen ring atom, and each of R⁸ and R⁹ is independently selected from -H, C₁₋₆alkyl, morpholinyl-C₁₋₃alkyl, pyrrolidinyl-C₁₋₃alkyl, and piperidinyl-C₁₋₃alkyl, wherein said C₁₋₆alkyl, morpholinyl-C₁₋₃alkyl, pyrrolidinyl-C₁₋₃alkyl, and piperidinyl-C₁₋₃alkyl are optionally substituted by one or more groups selected from halogen, methoxy, ethoxy, methyl, ethyl, hydroxy and -NR⁵R⁶; and

R⁴, R⁵ and R⁶ are independently selected from -H and C₁₋₃alkyl.

- 15 Compounds of the present invention may also be prepared according to the synthetic routes as depicted in Scheme 1.

Scheme 1.



R¹, R², R³ and R⁴ are as defined in the specifications.

Biological Evaluation**hCB₁ and hCB₂ receptor binding**

Human CB₁ receptor from Receptor Biology (hCB₁) or human CB₂ receptor
5 from BioSignal (hCB₂) membranes are thawed at 37 °C, passed 3 times through a 25-
gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5
mM EDTA, 5 mM MgCl₂, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots
containing the appropriate amount of protein are distributed in 96-well plates. The
IC₅₀ of the compounds of the invention at hCB₁ and hCB₂ are evaluated from 10-point
10 dose-response curves done with ³H-CP55,940 at 20000 to 25000 dpm per well (0.17-
0.21 nM) in a final volume of 300 µl. The total and non-specific binding are
determined in the absence and presence of 0.2 µM of HU210 respectively. The plates
are vortexed and incubated for 60 minutes at room temperature, filtered through
Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard
15 harvester using 3 mL of wash buffer (50 mM Tris, 5 mM MgCl₂, 0.5 mg BSA pH
7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a
TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

hCB₁ and hCB₂ GTPγS binding

20 Human CB₁ receptor from Receptor Biology (hCB₁) or human CB₂ receptor
membranes (BioSignal) are thawed at 37 °C, passed 3 times through a 25-gauge
blunt-end needle and diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM
NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM MgCl₂, pH 7.4, 0.1% BSA). The EC₅₀
and E_{max} of the compounds of the invention are evaluated from 10-point dose-
25 response curves done in 300µl with the appropriate amount of membrane protein and
100000-130000 dpm of GTPγ³⁵S per well (0.11 – 0.14 nM). The basal and maximal
stimulated binding is determined in absence and presence of 1 µM (hCB₂) or 10 µM
(hCB₁) Win 55,212-2 respectively. The membranes are pre-incubated for 5 minutes
with 56.25 µM (hCB₂) or 112.5 µM (hCB₁) GDP prior to distribution in plates (15
30 µM (hCB₂) or 30 µM (hCB₁) GDP final). The plates are vortexed and incubated for
60 minutes at room temperature, filtered on Unifilters GF/B (presoaked in water) with
the Tomtec or Packard harvester using 3 ml of wash buffer (50 mM Tris, 5 mM
MgCl₂, 50 mM NaCl, pH 7.0). The filters are dried for 1 hour at 55 °C. The

radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid. Antagonist reversal studies are done in the same way except that (a) an agonist dose-response curve is done in the presence of a constant concentration of antagonist, or (b) an antagonist dose-response curve is done in the presence of a constant concentration of agonist.

Based on the above assays, the dissociation constant (K_i) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$$K_i = IC_{50}/(1+[rad]/K_d),$$

Wherein IC_{50} is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that moment; and

K_d is the dissociation constant of the radioactive ligand towards the particular receptor.

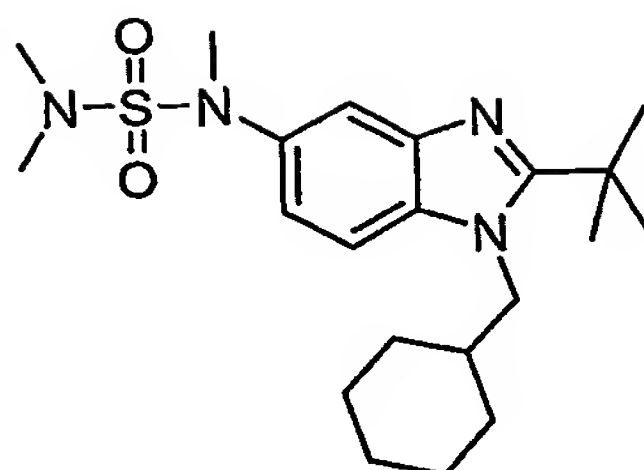
Using the above-mentioned assays, the K_i towards human CB_1 receptors for most compounds of the invention is measured to be in the range of 5 - 25 nM. The K_i towards human CB_2 receptors for most compounds of the invention is measured to be in the range of about 0.7 - 3.5 nM. The EC_{50} towards human CB_1 receptors for most compounds of the invention is measured to be in the range of about 24-84 nM. The E_{max} towards human CB_1 receptors for most compounds of the invention is measured to be in the range of about 105-116%.

EXAMPLES

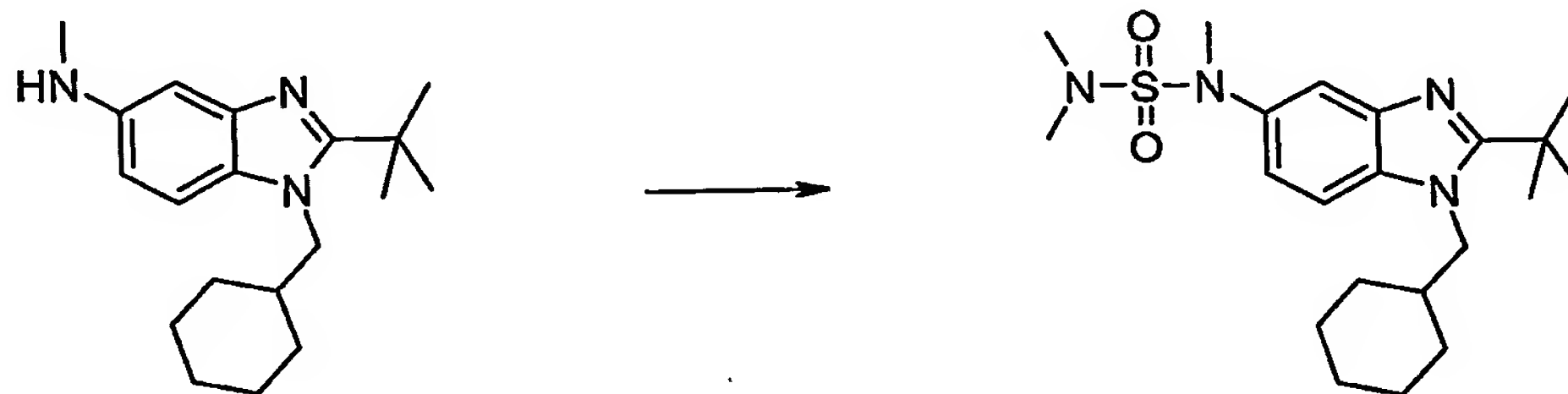
The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1

***N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N,N,N'*-trimethylsulfamide**

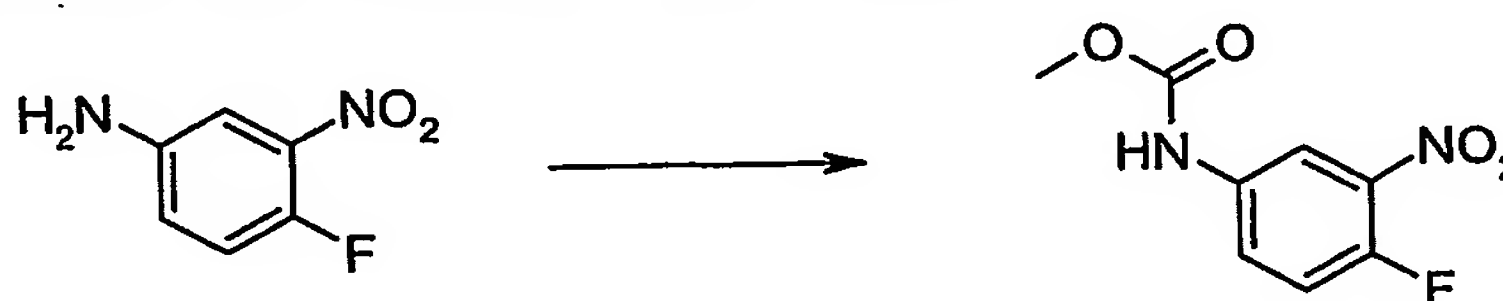


Step A. *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N,N',N'*-trimethylsulfamide



- 5 2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (40 mg, 0.133 mmol) (for preparation, see the following steps B, C, D, E and F) and dimethylsulfamoyl chloride (0.020 mL, 0.173 mmol) were stirred in 3 mL of dichloromethane containing a catalytic amount of DMAP overnight at rt. The solvent was evaporated. The product was purified by reversed-phase HPLC using 20-80%
 10 CH₃CN/H₂O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 36 mg (52%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.22 (m, 5H), 1.62 (m, 2H), 1.65 (s, 9H), 1.67 (m, 1H), 1.75 (m, 2H), 2.10 (m, 1H), 2.81 (s, 6H), 3.29 (s, 3H), 4.44 (d, *J* = 7.62 Hz, 2H), 7.64 (dd, *J* = 9.08, 2.05 Hz, 1H), 7.78 (d, *J* = 1.95 Hz, 1H), 7.90 (d, *J* = 8.98 Hz, 1H); MS (ESI) (*M*+*H*)⁺ 407.3; Anal. Calcd for
 15 C₂₁H₃₄N₄O₂S + 1.3 TFA + 0.3 H₂O: C, 50.60; H, 6.46; N, 10.00. Found: C, 50.64; H, 6.47; N, 10.15.

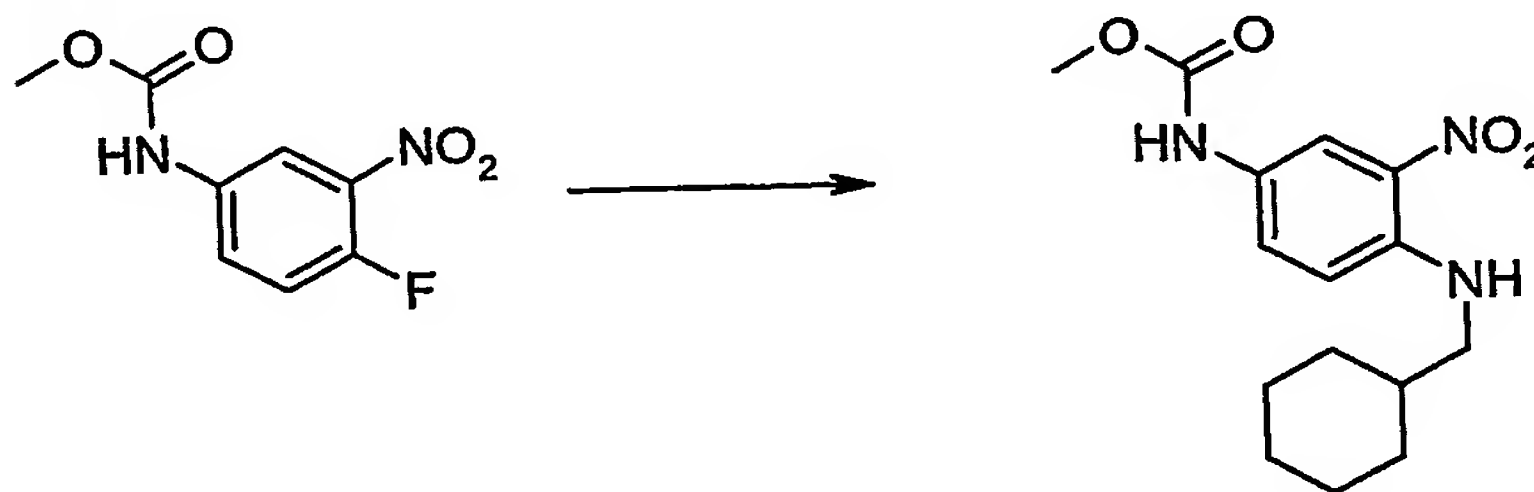
Step B. Methyl (4-fluoro-3-nitrophenyl)carbamate



- 20 Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol) and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight.

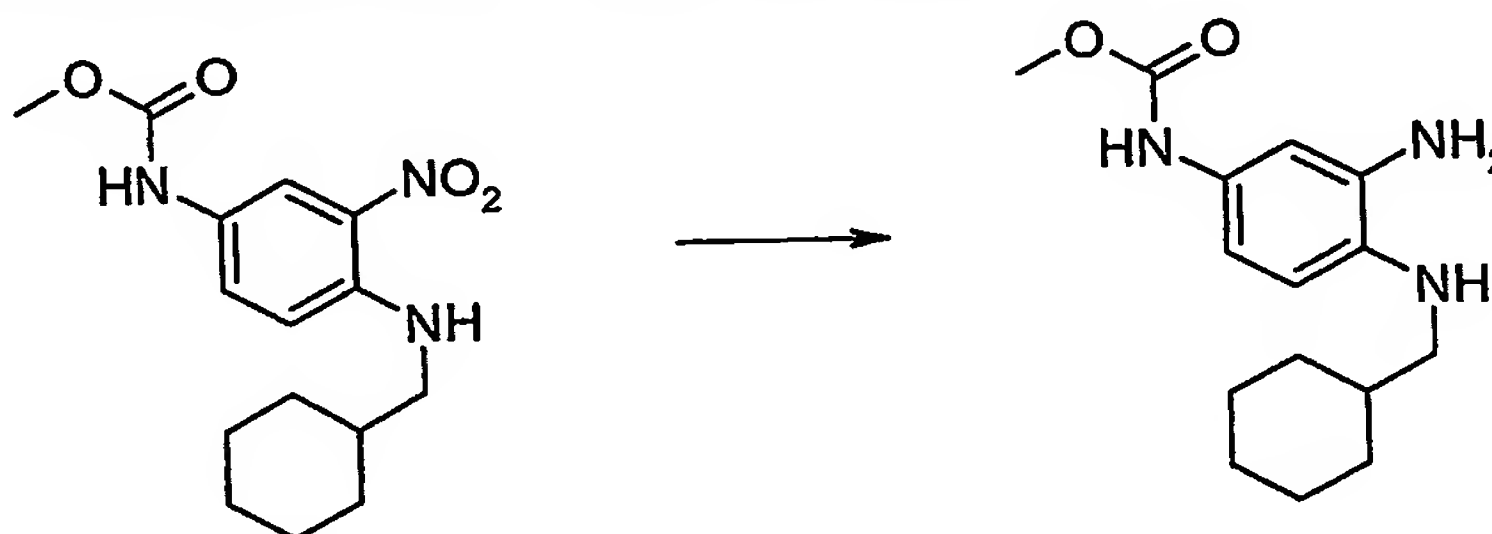
The solution was then diluted with 200 mL of dichloromethane and washed with 2M HCl, brine and dried over anhydrous MgSO_4 . The solvent was concentrated and the product was directly used for next step without further purification. Yield: 35.5 g (99%); ^1H NMR (400 MHz, CHCl_3 - d) δ 3.81 (s, 3H), 7.02 (s, 1H), 7.23 (m, 1H), 7.72 (d, $J = 8.59$ Hz, 1H), 8.17 (dd, $J = 6.35, 2.64$ Hz, 1H).

Step C. Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate



Methyl (4-fluoro-3-nitrophenyl)carbamate (1.00 g, 4.67 mmol) and cyclohexylmethyl amine (0.730 mL, 5.60 mmol) were stirred in EtOH (20 mL) containing TEA (1.0 mL, 7.00 mmol) at 75°C for 24h. The solvent was concentrated. The residue was dissolved in EtOAc and washed with 5% KHSO_4 solution, saturated NaHCO_3 solution, brine and dried over anhydrous MgSO_4 . The crude product was purified by flash chromatography using 4:1/hex:EtOAc on silica gel. Yield: 1.05 g (73%); ^1H NMR (400 MHz, CHCl_3 - d) δ 1.04 (ddd, $J = 24.02, 12.11, 2.93$ Hz, 2H), 1.25 (m, 3H), 1.69 (m, 2H), 1.76 (m, 1H), 1.79 (m, 1H), 1.83 (m, 1H), 1.86 (m, 1H), 3.14 (dd, $J = 6.44, 5.66$ Hz, 2H), 3.78 (s, 3H), 6.46 (m, 1H), 6.84 (d, $J = 9.37$ Hz, 1H), 7.63 (m, 1H), 8.05 (d, $J = 2.54$ Hz, 1H), 8.09 (m, 1H).

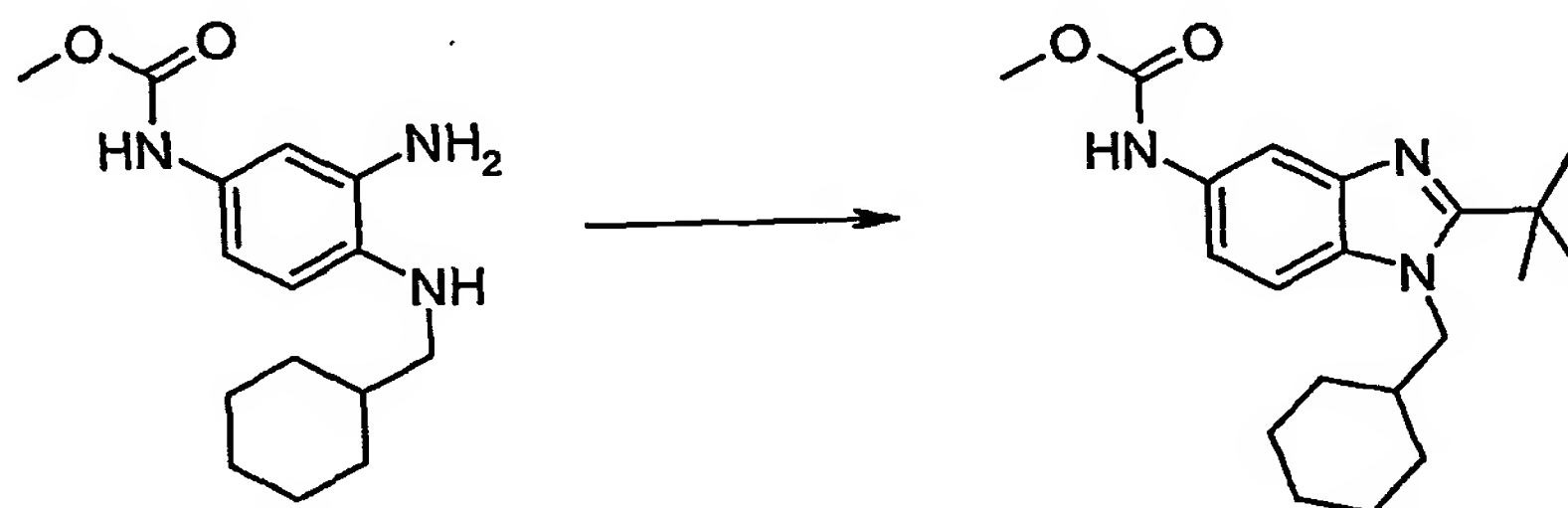
Step D. Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate



Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate (1.05 g, 3.42 mmol) was dissolved in 30 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under H_2 atmosphere (40 psi)

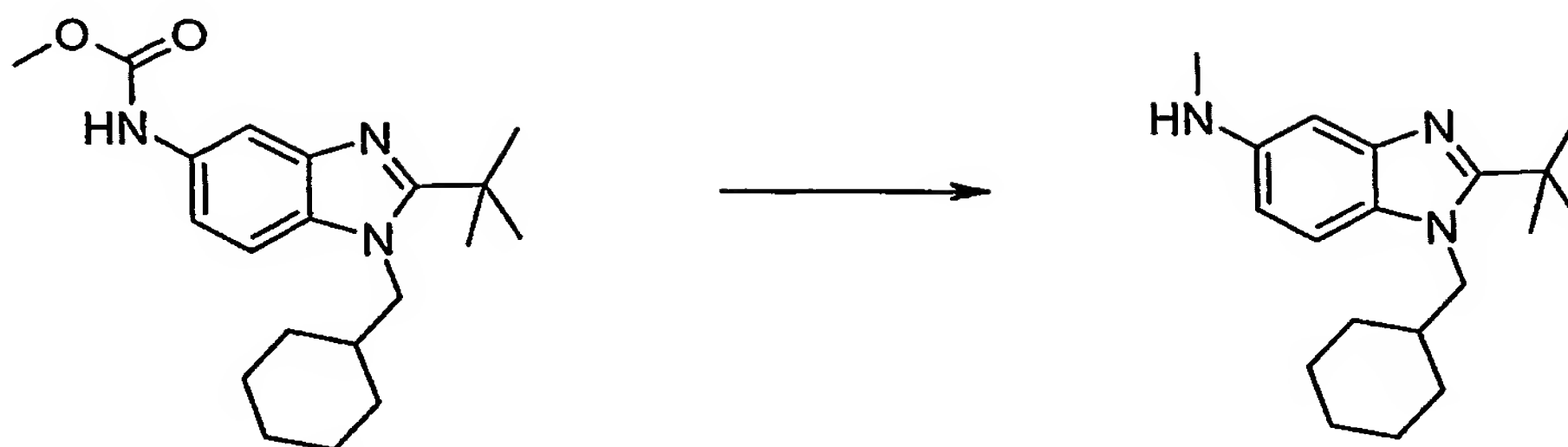
at rt overnight. The solution was filtered through Celite and the solvent evaporated. The product was directly used for the next step without further purification. Yield: 950 mg (99%). MS (ESI) (M+H)⁺ 277.9.

5 **Step E. Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbamate**



Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl} carbamate (950 mg, 3.43 mmol) and DMAP (100 mg, 0.858 mmol) were dissolved in 25 mL of
 10 dichloromethane. Trimethylacetyl chloride (0.460 mL, 3.77 mmol) was added in dropwise and the solution was stirred at rt for 1h. The solvent was concentrated. The residue was divided in two portions and each of them was dissolved in 3 mL of glacial AcOH in a sealed tube. The solutions were heated at 150°C using a Personal Chemistry Smith Synthesizer microwave instrument for three intervals of 30 min (3 X
 15 30 min). The contents of the two tubes were combined and the solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by flash chromatography using 3:1/dichloromethane:diethyl ether. Yield: 656 mg (56%);
 20 ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.08 (m, 2H), 1.18 (m, 3H), 1.54 (s, 9H), 1.65 (m, 1H), 1.69 (m, 2H), 1.73 (dd, J = 5.96, 3.22 Hz, 2H), 2.02 (m, 1H), 3.78 (s, 3H), 4.10 (d, J = 7.42 Hz, 2H), 6.64 (m, 1H), 7.25 (d, J = 8.79 Hz, 1H), 7.39 (m, 1H), 7.59 (d, J = 1.76 Hz, 1H).

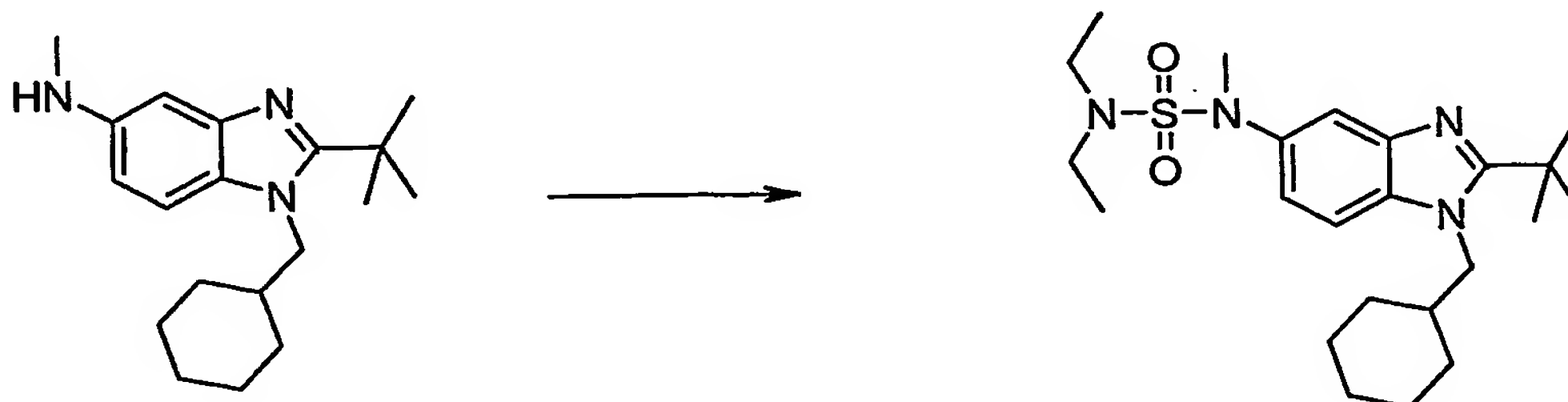
Step F. 2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine



Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbamate (650 mg, 1.89 mmol) was dissolved in 20 mL of THF at 0°C under nitrogen. 1M HCl/ether (2.65 mL, 2.65 mmol) was added dropwise and the solution was stirred at 0°C for 15 min. LiAlH₄ (360 mg, 9.45 mmol) was then slowly added and the solution was stirred at rt overnight. The reaction mixture was quenched at 0°C by addition of MeOH (5 mL) followed by water (10 mL). The solution was diluted with EtOAc and washed with saturated NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated and the product was used directly for Step A without further purification. Yield: 544 mg (96%). ¹H NMR (400 MHz, CHLOROFORM-D) δ 1.08 (s, 2H), 1.17 (m, 3H), 1.54 (s, 9H), 1.64 (m, 2H), 1.67 (m, 2H), 1.72 (m, 2H), 2.02 (m, 1H), 2.87 (s, 3H), 4.06 (d, J = 7.62 Hz, 2H), 6.60 (dd, J = 8.69, 2.25 Hz, 1H), 7.00 (d, J = 1.76 Hz, 1H), 7.12 (d, J = 8.59 Hz, 1H).

Example 2

***N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*',*N*'-diethyl-*N*-methylsulfamide**



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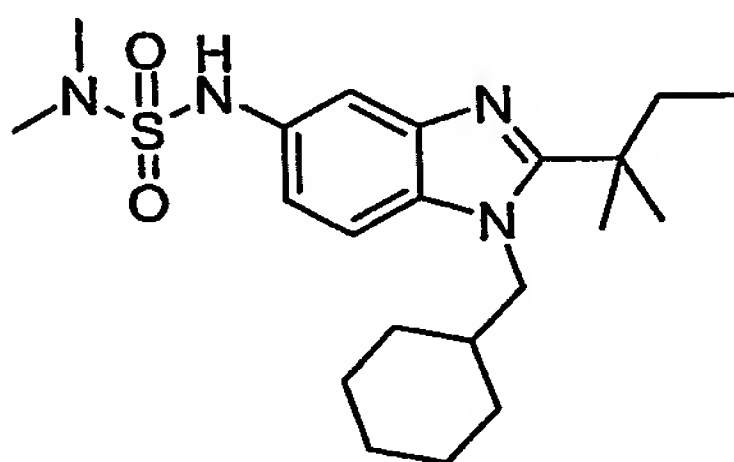
A solution of diethylamine (0.103 mL, 1.00 mmol) in 1 mL dichloromethane and TEA (0.140 mL, 1.00 mmol) were added sequentially to a cold (0°C) solution of SO₂Cl₂ (0.160 mL, 2.00 mmol) in dichloromethane (1 mL) under a nitrogen atmosphere. The solution was then stirred at rt for 3h. The solution was washed with 5% KHSO₄ solution, brine and dried over anhydrous MgSO₄. The solvent was

25

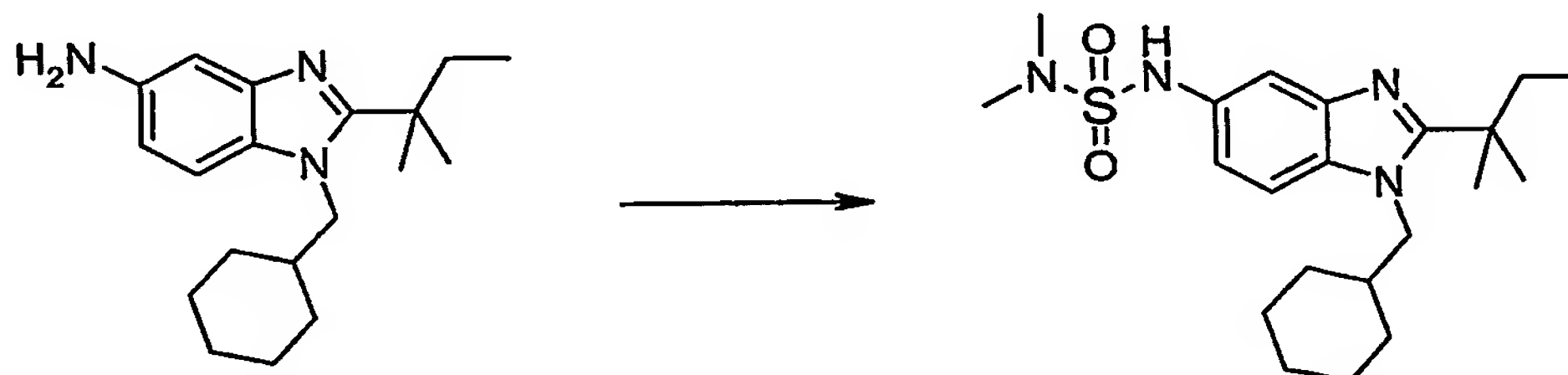
concentrated. The residue was then dissolved in 1 mL of dichloromethane, to which a solution of 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (25 mg, 0.0835 mmol) and DMAP (catalytic) in 1 mL of dichloromethane was added dropwise. The solution was stirred at rt for 24h. The product was purified by
 5 reversed-phase HPLC using 30-80% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 15 mg (33%); ¹H NMR (400 MHz, METHANOL-D₄) δ 1.13 (t, J = 7.13Hz, 6H), 1.24 (m, 5H), 1.63 (m, 2H), 1.67 (s, 9H), 1.70 (m, 1H), 1.77 (m, 2H), 2.12 (m, 1H), 3.26 (s, 3H), 3.30 (m, 4H), 4.46 (d, J = 7.62Hz, 2H), 7.61 (dd, J = 8.98, 2.15Hz, 1H), 7.78 (d, J = 1.95 Hz, 1H), 7.89 (d, J =
 10 8.98Hz, 1H); MS (ESI) (M+H)⁺ 435.2; Anal. Calcd for C₂₃H₃₈N₄O₂S + 1.2 TFA + 0.8 H₂O: C, 52.07; H, 7.02; N, 9.56. Found: C, 52.00; H, 7.01; N, 9.55.

Example 3

***N'*-[1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-yl]-*N,N*-dimethyl-sulfamide**
 15



Step A. *N'*-[1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-yl]-*N,N*-dimethyl-sulfamide

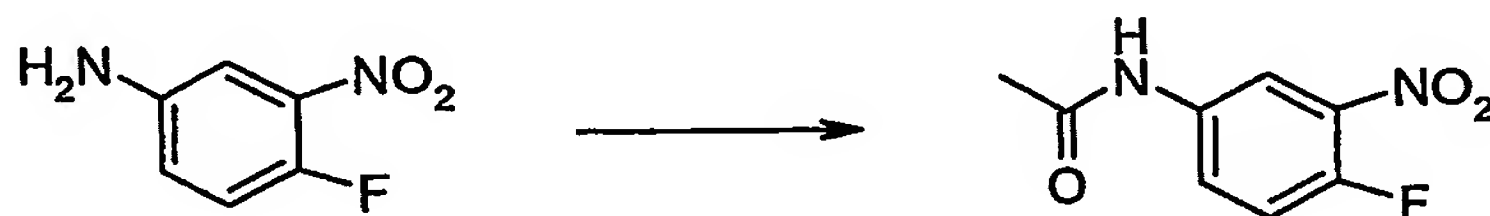


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DMAP (80.1 mg, 0.65 mmol) was added to a solution of 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-amine (69.5 mg, 0.18 mmol) (for preparation, see the following steps B, C, D, E and F) in acetonitrile (10 mL) at 0 °C,

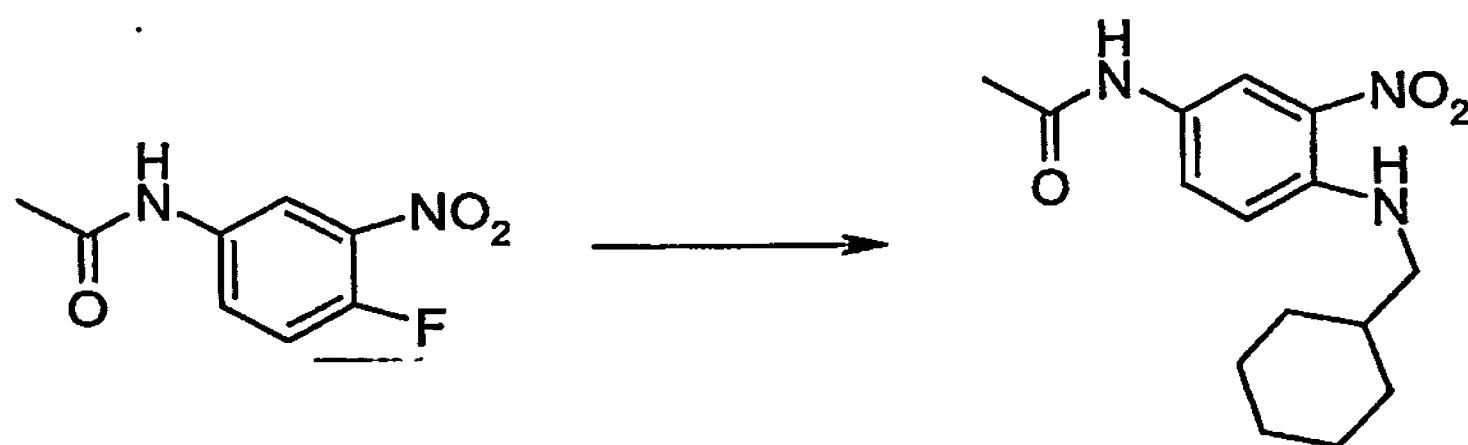
followed by addition of dimethylsulfamoyl chloride (22 μ L, 28.7 mg, 0.20 mmol). The resulting mixture was heated at reflux for 20 h and then quenched with MeOH (2 mL). After evaporation of the solvent, the residue was dissolved in EtOAc (100 mL) and washed with NaCl aqueous solution (10 mL) and dried over Na₂SO₄. After
5 filtration and evaporation, the residue was purified by MPLC (hexanes/EtOAc 1:1 as eluent on silica gel) to give the title compound as a white solid (56.2 mg, 76%), which was converted to a white solid as a TFA salt. ¹H NMR (400 MHz, CD₃OD): δ 0.84 (t, J=7.52 Hz, 3 H), 1.24 (m, 5 H), 1.64 (m, 2 H), 1.66 (s, 6 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.01 (q, J=7.55 Hz, 2 H), 2.11 (m, 1 H), 2.82 (s, 6 H), 4.44 (d, J=7.81 Hz, 2 H),
10 7.37 (dd, J=8.98, 2.15 Hz, 1 H), 7.69 (d, J=2.15 Hz, 1 H), 7.84 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺: 407.3; Anal. Calcd for C₂₁H₃₄N₄O₂S + 1.0 TFA + 0.2 H₂O: C, 52.70; H, 6.81; N, 10.69. Found: C, 52.70; H, 6.66; N, 10.45.

Step B. N-(4-fluoro-3-nitrophenyl)acetamide



15 4-Fluoro-3-nitro-aniline (45.0 g, 288.2 mmol) was added portionwise to acetic anhydride (150 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The white solid was collected and dried *in vacuo* to give the title compound (42.0 g, 70%). ¹H NMR (400 MHz, CDCl₃): δ 2.23 (s, 3 H), 7.26 (m, 1 H), 7.50 (s broad, 1 H), 7.87 (m, 1 H), 8.23 (dd, J=6.44, 2.73 Hz, 1 H).
20

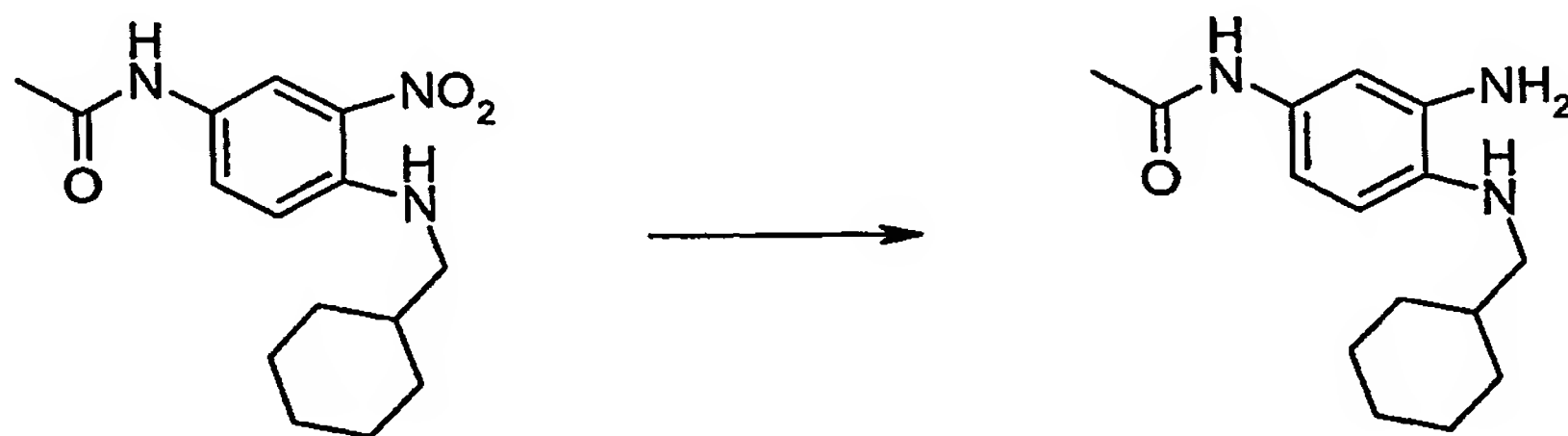
Step C. N-{4-[(cyclohexylmethyl)amino]-3-nitrophenyl}acetamide



25 Cyclohexylmethylamine (2.86 mL, 2.49 g, 22.0 mmol) was added to a mixture of N-(4-fluoro-3-nitrophenyl)acetamide (3.96 g, 20.0 mmol) and sodium carbonate (4.66 g, 44 mmol) in EtOH (50 mL) at room temperature. The reaction mixture was heated for

48 h at 60 °C, and diluted with H₂O (800 mL). The orange solid was precipitated out and collected to give the desired product (6.60 g, 100%). MS (ESI) (M+H)⁺: 292.32.

Step D. *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}acetamide

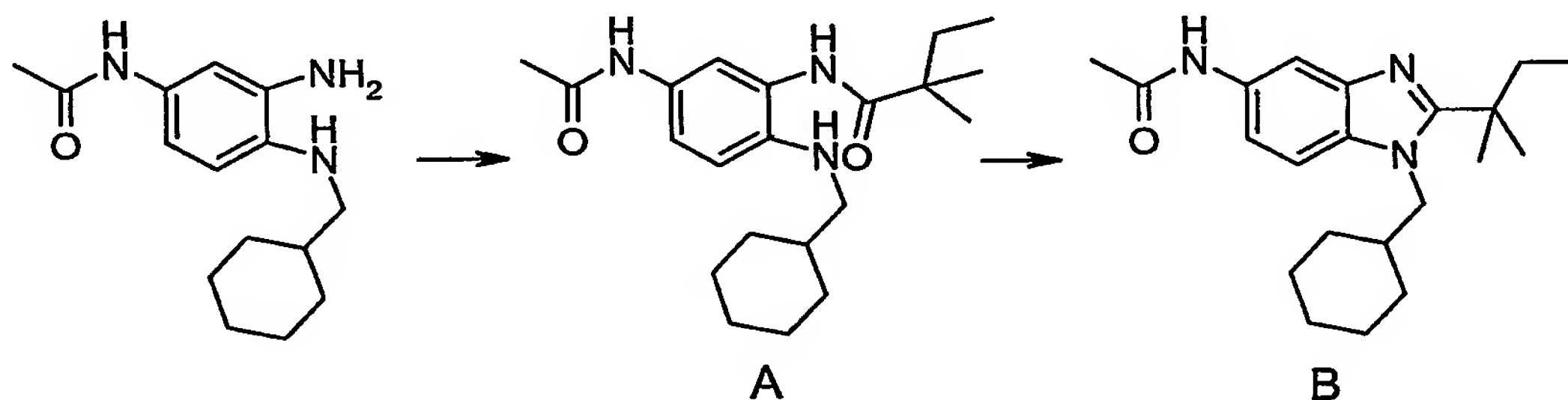


5

The above crude product *N*-{4-[(cyclohexylmethyl)amino]-3-nitrophenyl}acetamide (6.60 g) was hydrogenated in ethyl acetate (300 mL) catalyzed by 10% Pd/C (0.5 g) at 20-30 psi H₂ in Parr shaker for 4.5 h at room temperature. After filtration through celite and concentration, 5.08 g (97%) of a purple solid was obtained. which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 1.00 (m, 2 H), 1.24 (m, 3 H), 1.59 (m, 2 H), 1.72 (m, 2 H), 1.84 (m, 2 H), 2.13 (s, 3 H), 2.91 (d, *J*=6.64 Hz, 2 H), 3.37 (s broad, 3 H), 6.56 (d, *J*=8.40 Hz, 1 H), 6.69 (dd, *J*=8.30, 2.25 Hz, 1 H), 6.98 (s, 1 H), 7.12 (d, *J*=2.34 Hz, 1 H). MS (ESI) (M+H)⁺: 262.31.

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Step E. *N*-[1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1*H*-benzimidazol-5-yl]acetamide



A

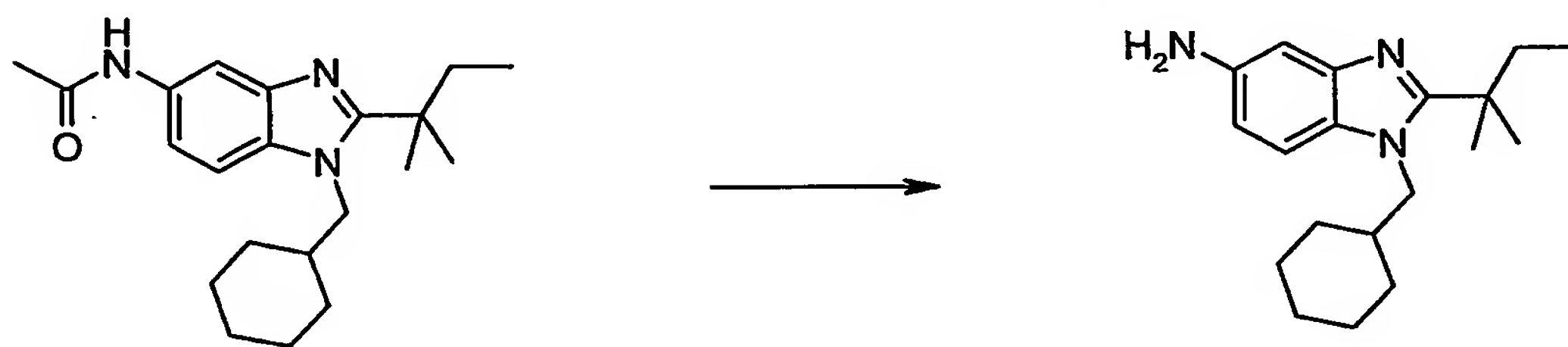
B

DMAP (0.65 g, 5.3 mmol) was added to a suspension of *N*-{3-amino-4-[(cyclohexylmethyl)amino]phenyl}acetamide (2.09 g, 8.0 mmol) in dichloromethane (40 mL) at -10 °C, followed by addition of 2,2-dimethylbutyryl chloride (1.51 g, 11.2 mmol). The resulting mixture was stirred overnight at room temperature. After evaporation of the solvent, 4.14 g of a brown solid was obtained, which was consistent with the desired coupling product A. MS (ESI) (M+H)⁺ = 360.07.

20

308.1 mg of the above crude product A was dissolved in 1,2-dichloroethane (5 mL) in a Teflon-capped test tube. The vessel was irradiated by microwave for 3 h at 170 °C. Upon evaporation of the solvent, the residue was dissolved in EtOAc (100 mL), washed with 2N NaOH aqueous solution (10 mL), saturated NaCl aqueous solution (10 mL) and dried over Na₂SO₄. After filtration and evaporation, the residue was purified by MPLC (hexanes/EtOAc 1:1 as eluent on silica gel) to give the title compound as a light yellow solid (111.0 mg, 55%), which was converted to a white solid as a TFA salt. ¹H NMR (400 MHz, CD₃OD): δ 0.84 (t, J=7.52 Hz, 3 H), 1.25 (m, 5 H), 1.63 (m, 2 H), 1.66 (s, 6 H), 1.70 (m, 1 H), 1.77 (m, 2 H), 2.01 (q, J=7.42 Hz, 2 H), 2.10 (m, 1 H), 2.18 (s, 3 H), 4.44 (d, J=7.81 Hz, 2 H), 7.50 (dd, J=8.98, 1.95 Hz, 1 H), 7.84 (d, J=9.18 Hz, 1 H), 8.44 (d, J=1.76 Hz, 1 H). MS (ESI) (M+H)⁺: 342.05.

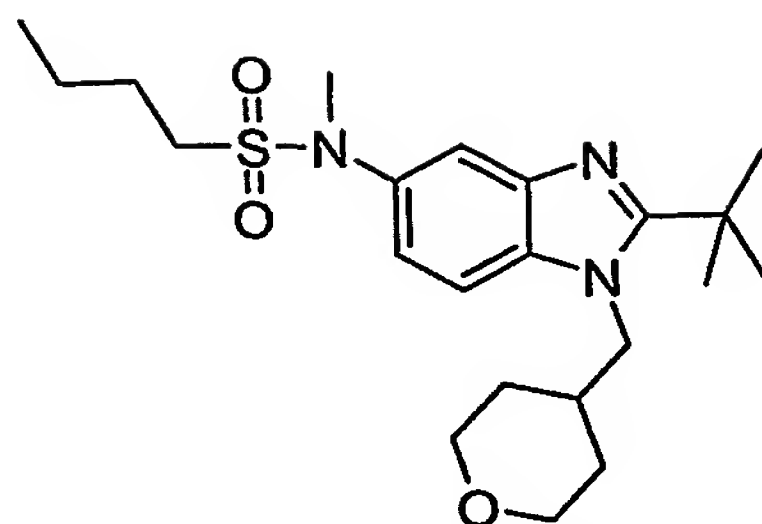
Step F. 1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1H-benzimidazol-5-amine



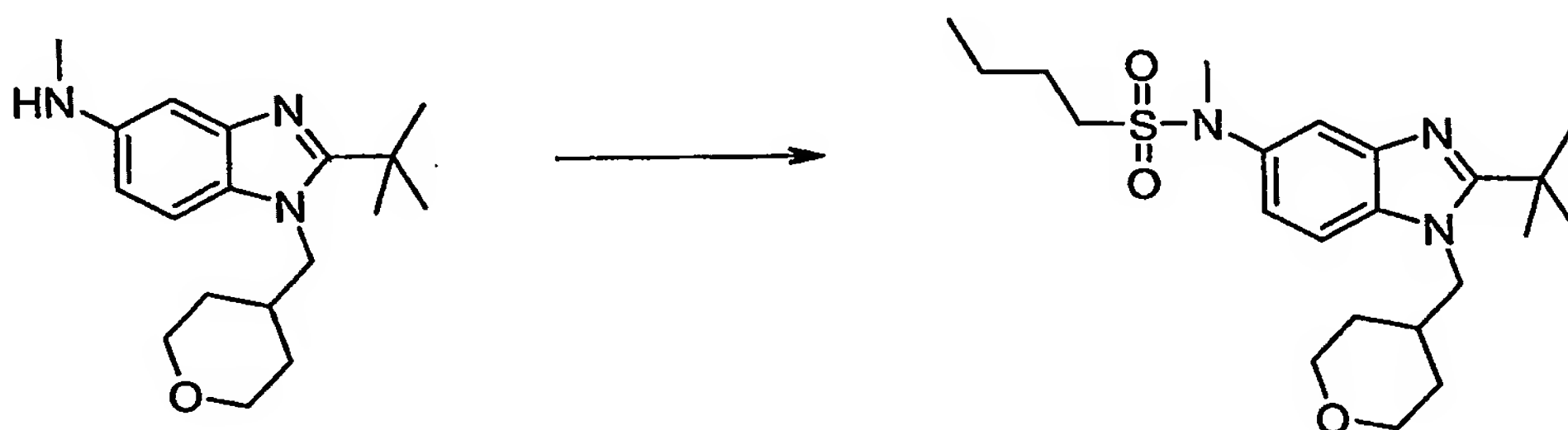
N-[1-(cyclohexylmethyl)-2-(1,1-dimethylpropyl)-1H-benzimidazol-5-yl]acetamide (110.0 mg, 0.32 mmol) was dissolved in EtOH (3 mL) and 2N HCl (2 mL) in a Teflon-capped test tube. The vessel was irradiated by microwave for 45 min. at 120 °C. Upon evaporation of the solvent, the title compound was obtained as a grey white solid (117.8 mg, 100%). ¹H NMR (400 MHz, CD₃OD): δ 0.87 (t, J=7.52 Hz, 3 H), 1.27 (m, 5 H), 1.66 (m, 3 H), 1.71 (s, 6 H), 1.78 (m, 2 H), 2.05 (q, J=7.42 Hz, 2 H), 2.13 (m, 1 H), 4.53 (d, J=7.62 Hz, 2 H), 7.66 (dd, J=8.79, 1.56 Hz, 1 H), 7.97 (d, J=1.76 Hz, 1 H), 8.17 (d, J=8.79 Hz, 1 H); MS (ESI) (M+H)⁺: 300.05.

Example 4

N-[2-*tert*-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-*N*-methylbutane-1-sulfonamide

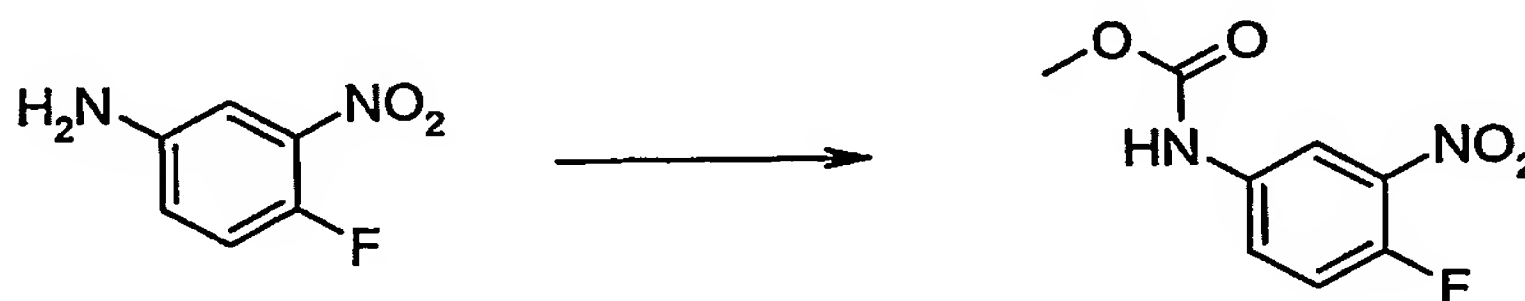


Step A: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylbutane-1-sulfonamide



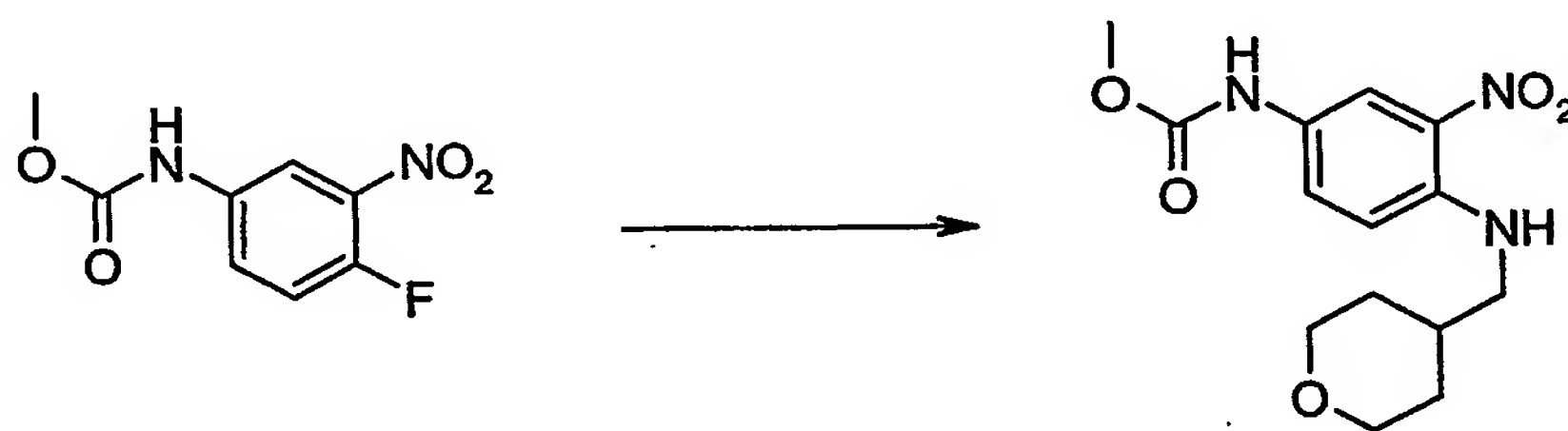
- 5 2-*tert*-Butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (for preparation see following Steps B, C, D, E and F) (38 mg, 0.126 mmol) and 1-butan-1-ylsulfonyl chloride (0.025 mL, 0.189 mmol) were stirred in 3 mL of DCM containing a catalytic amount of DMAP at rt overnight. The solvent was evaporated and the product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 39 mg (58%). ¹H NMR (400 MHz, METHANOL-D₄): δ 0.88 - 0.94 (m, *J*=7.42, 7.42 Hz, 3 H), 1.43 (dq, *J*=15.06, 7.41 Hz, 2 H), 1.53 - 1.59 (m, 2 H), 1.59 - 1.66 (m, 2 H), 1.69 (s, 9 H), 1.71 - 1.77 (m, 2 H), 2.35 - 2.42 (m, 1 H), 3.10 - 3.16 (m, 2 H), 3.35 (dt, *J*=11.52, 2.73 Hz, 2 H), 3.40 (s, 3 H), 3.93 (d, *J*=3.12 Hz, 1 H), 3.96 (d, *J*=3.71 Hz, 1 H), 4.54 (d, *J*=7.42 Hz, 2 H), 7.69 (dd, *J*=8.98, 2.15 Hz, 1 H), 7.81 (d, *J*=1.56 Hz, 1 H), 7.97 (d, *J*=8.98 Hz, 1 H); MS (ESI) (*M*+*H*)⁺ 422.2; Anal. Calcd for C₂₂H₃₅N₃O₃S + 1.3 TFA + 1.2 H₂O: C, 49.96; H, 6.60; N, 7.10. Found: C, 49.98; H, 6.67; N, 6.83.

Step B: Methyl (4-fluoro-3-nitrophenyl)carbamate



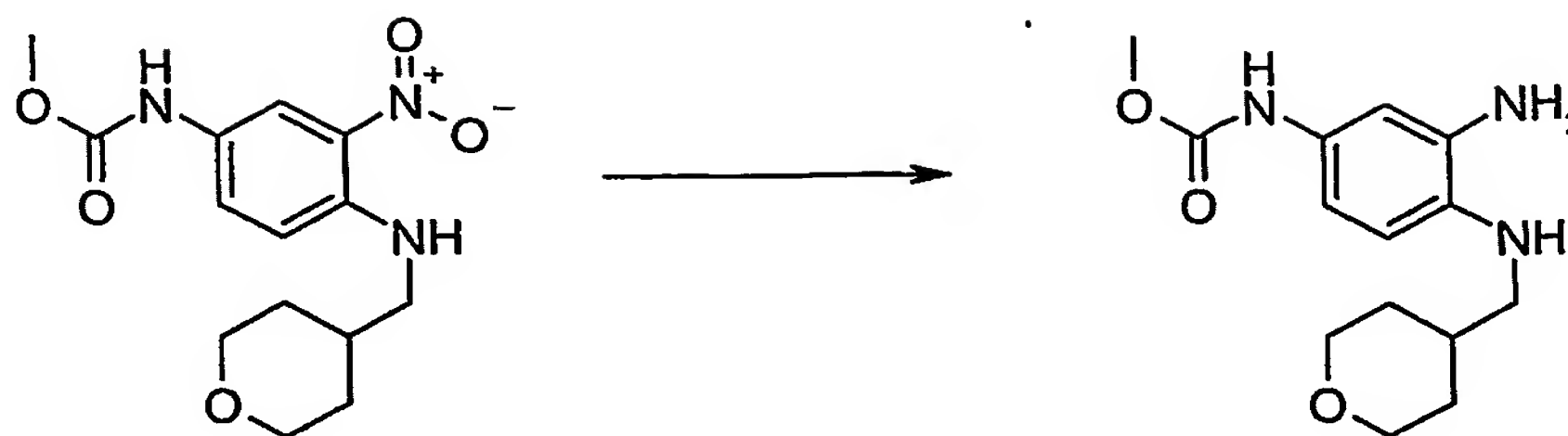
Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol) and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight. The solution was then diluted with 200 mL of dichloromethane and washed with 2M HCl, brine and dried over anhydrous MgSO₄. The solvent was concentrated and the product was directly used for next step without further purification. Yield: 35.5 g (99%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 3.81 (s, 3H), 7.02 (s, 1H), 7.23 (m, 1H), 7.72 (d, J = 8.59Hz, 1H), 8.17 (dd, J = 6.35, 2.64Hz, 1H).

Step C: Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate



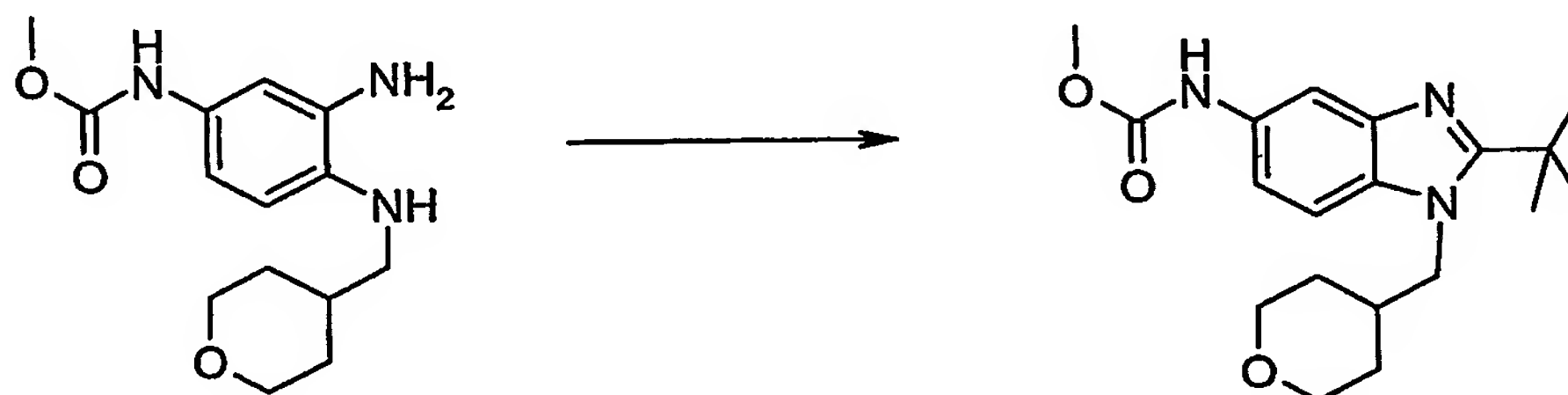
Methyl (4-fluoro-3-nitrophenyl)carbamate (2.0g, 9.32 mmol) and 4-aminomethyl tetrahydropyran (1.28g, 11.2 mmol) were stirred in 50 mL of EtOH containing TEA (2.0 mL, 14.0 mmol) at 75°C for 48h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous 5% KHSO₄, saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes : EtOAc as eluent. Yield: 2.53g (88%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.42 (ddd, J=25.24, 12.06, 4.49 Hz, 2 H), 1.73 (d, J=1.76 Hz, 1 H), 1.76 (d, J=1.95 Hz, 1 H), 1.88 - 2.01 (m, 1 H), 3.22 (dd, J=6.74, 5.57 Hz, 2 H), 3.42 (td, J=11.86, 2.05 Hz, 2 H), 3.78 (s, 3 H), 4.01 (d, J=4.30 Hz, 1 H), 4.04 (d, J=3.51 Hz, 1 H), 6.48 (br.s, 1 H), 6.85 (d, J=9.37 Hz, 1 H), 7.65 (br.s, 1 H), 8.03 - 8.09 (m, 2 H).

Step D: Methyl {3-amino-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate



Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl} carbamate (2.53g, 8.18 mmol) was dissolved in 50 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under H₂ atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 2.29g (99%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.40 (ddd, *J*=25.09, 12.01, 4.49 Hz, 2 H), 1.70 - 1.74 (m, 1 H), 1.74 - 1.77 (m, 1 H), 1.81 - 1.92 (m, 1 H), 2.99 (d, *J*=6.64 Hz, 2 H), 3.34 (br.s, 2 H), 3.41 (dt, *J*=11.81, 2.15 Hz, 2 H), 3.74 (s, 3 H), 3.99 (d, *J*=3.51 Hz, 1 H), 4.02 (d, *J*=3.51 Hz, 1 H), 6.38 (br.s, 1 H), 6.55 - 6.60 (m, 1 H), 6.62 - 6.68 (m, 1 H), 6.95 (br.s, 1 H).

Step E: Methyl [2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate

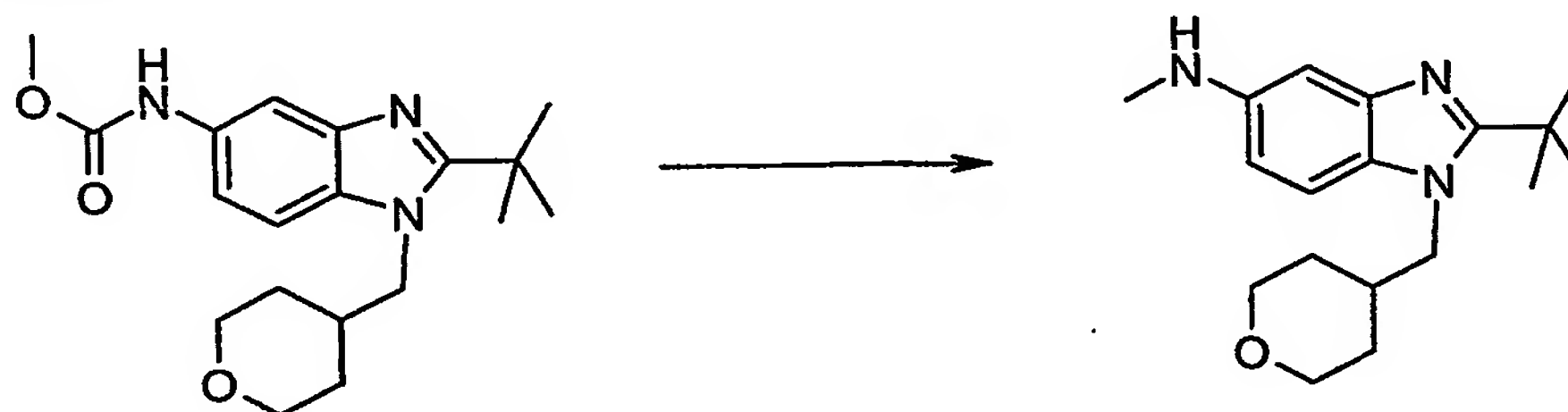


Methyl {3-amino-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl} carbamate (2.29 g, 8.20 mmol) and DMAP (0.20 g, 1.64 mmol) were dissolved in 75 mL of DCM. Trimethylacetyl chloride (1.10 mL, 9.02 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The residue was dissolved in 25 mL of AcOH and was heated at 125°C for 1h using a Personal Chemistry microwave apparatus. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 4:3 / hexanes :

acetone as eluent. Yield: 1.81g (64%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.48 - 1.54 (m, 4 H) 1.56 (s, 9 H) 2.23 - 2.35 (m, 1 H) 3.27 - 3.35 (m, 2 H) 3.78 (s, 3 H) 3.96 (t, *J*=2.93 Hz, 1 H) 3.99 (t, *J*=3.03 Hz, 1 H) 4.18 (d, *J*=7.42 Hz, 2 H) 6.63 (br.s, 1 H) 7.24 - 7.28 (m, 1 H) 7.41 (br.s, 1 H) 7.61 (d, *J*=1.95 Hz, 1 H).

5

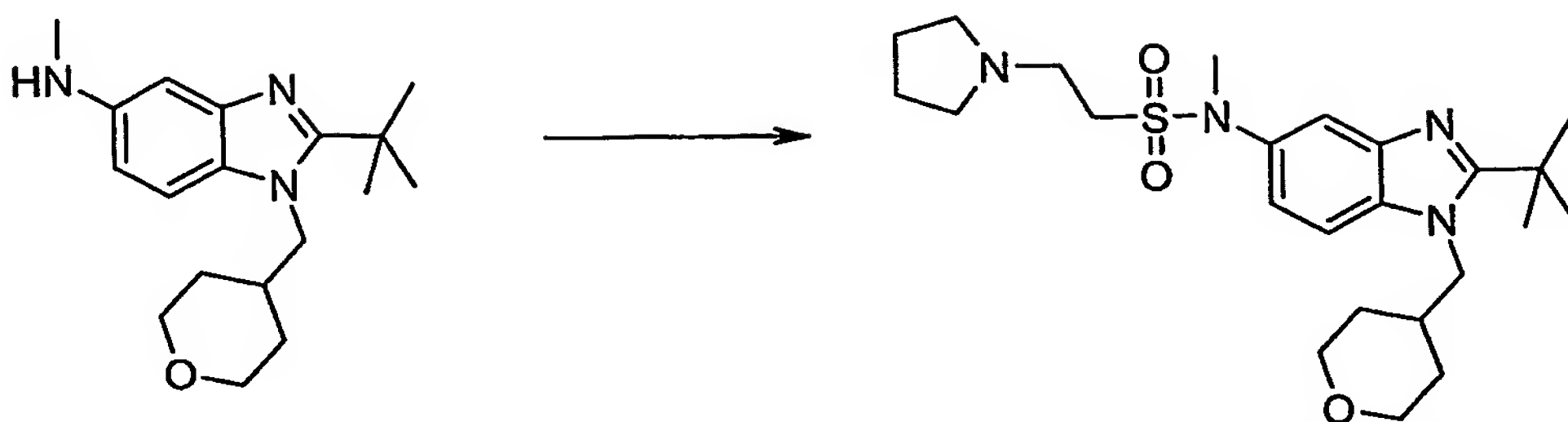
Step F: 2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine



- Methyl [2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate (1.80 g, 5.21 mmol) was dissolved in 75 mL of THF at 0°C. 1M HCl/ether (7.3 mL, 7.29 mmol) was added dropwise and the solution was stirred at 0°C for 15 min. LiAlH₄ (988 mg, 26.1 mmol) was added slowly and the solution was stirred at rt overnight. The reaction was quenched at 0°C by the addition of MeOH (5 mL) followed by water (10 mL) and the solution was left to stir at rt for 30 min.
- Anhydrous Na₂SO₄ (10 g) was added and the solution was stirred at rt for another 30 min. The solution was filtered and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was evaporated. Yield: 1.54g (98%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.49 - 1.53 (m, 4 H), 1.53 - 1.57 (m, 9 H), 2.22 - 2.32 (m, 1 H), 2.87 (s, 3 H), 3.26 - 3.35 (m, 2 H), 3.95 (t, *J*=3.03 Hz, 1 H), 3.97 - 4.00 (m, 1 H), 4.13 (d, *J*=7.42 Hz, 2 H), 6.61 (dd, *J*=8.59, 2.15 Hz, 1 H), 6.99 (d, *J*=1.95 Hz, 1 H), 7.11 (d, *J*=8.59 Hz, 1 H).

Example 5:

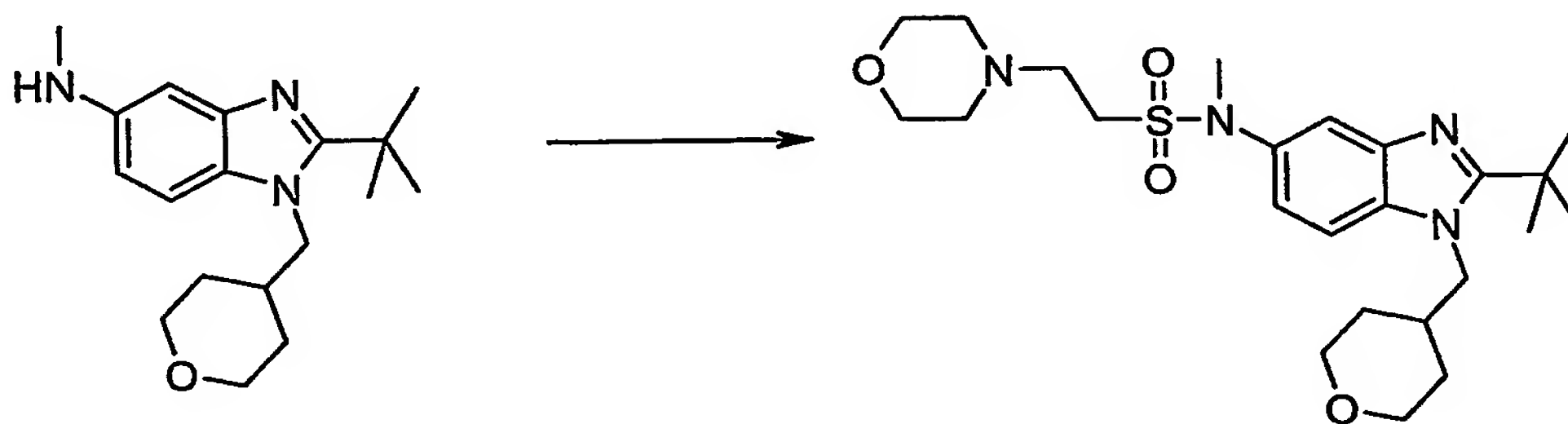
- N-[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methyl-2-pyrrolidin-1-ylethanesulfonamide**



- 2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (30 mg, 0.0996 mmol) was dissolved in 2 mL of DCE containing pyridine (0.012 mL, 0.149 mmol). 2-Chloro-1-ethanesulfonyl chloride (0.012 mL, 0.129 mmol) was added and the solution was stirred at rt for 3h. Pyrrolidine (0.080 mL, 0.996 mmol) was added and the solution was stirred at rt for 3h. The solution was washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 44 mg (77%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.50 - 1.56 (m, 2 H), 1.56 - 1.64 (m, 2 H), 1.68 (s, 9 H), 2.00 - 2.08 (m, 2 H), 2.09 - 2.20 (m, 2 H), 2.32 - 2.43 (m, 1 H), 3.06 - 3.21 (m, 2 H), 3.35 (td, J=11.67, 2.25 Hz, 2 H), 3.45 (s, 3 H), 3.63 - 3.77 (m, 6 H), 3.93 (d, J=3.12 Hz, 1 H), 3.96 (d, J=3.12 Hz, 1 H), 4.53 (d, J=7.62 Hz, 2 H), 7.66 (dd, J=8.98, 1.95 Hz, 1 H), 7.84 (d, J=1.56 Hz, 1 H), 7.95 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 463.1.

Example 6:

***N*-[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methyl-2-morpholin-4-ylethanesulfonamide**

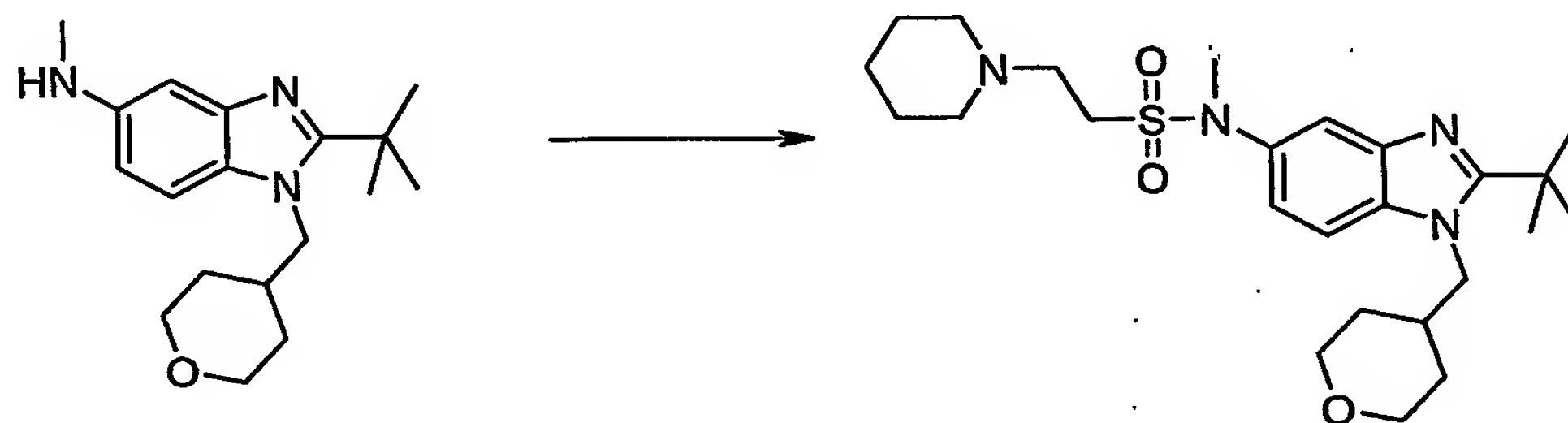


Following the same procedure as in Example 5 using 2-tert-butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (36 mg, 0.119 mmol), 2-chloro-1-ethanesulfonyl chloride (0.015 mL, 0.143 mmol), pyridine (0.015 mL, 0.179 mmol) and morpholine (0.050 mL, 0.595 mmol) in 3 mL of DCE. The product

was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 42 mg (50%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.51 - 1.57 (m, 2 H), 1.58 - 1.66 (m, 2 H), 1.69 (s, 9 H), 2.33 - 2.42 (m, 1 H), 3.31 - 3.40 (m, 4 H), 3.45 (s, 3 H), 3.57 - 3.63 (m, 2 H), 3.68 - 3.75 (m, 2 H), 3.89 (br.s, 2 H), 3.93 (d, J=3.51 Hz, 1 H), 3.96 (d, J=2.34 Hz, 1 H), 4.55 (d, J=7.62 Hz, 2 H), 7.70 (dd, J=8.98, 1.95 Hz, 1 H), 7.86 (d, J=2.15 Hz, 1 H), 7.99 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 479.0; Anal. Calcd for C₂₄H₃₈N₄O₄S + 2.5 TFA + 1.0 H₂O: C, 44.56; H, 5.48; N, 7.17. Found: C, 44.53; H, 5.38; N, 7.26.

10 Example 7

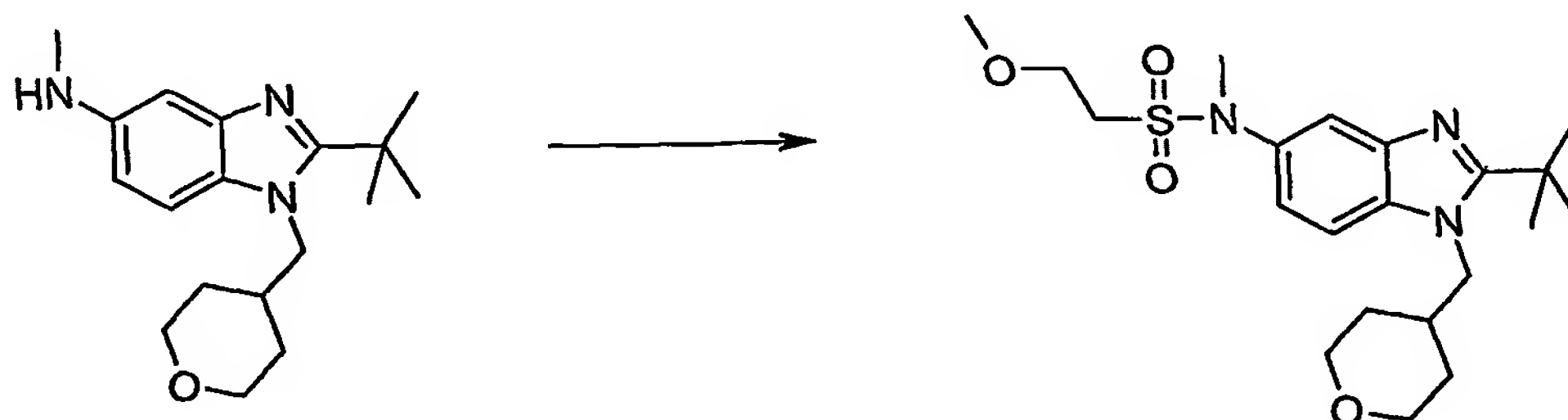
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-2-piperidin-1-ylethanesulfonamide**



Following the same procedure as in Example 5 using 2-*tert*-butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (130 mg, 0.431 mmol), 2-chloro-1-ethanesulfonyl chloride (0.054 mL, 0.517 mmol), pyridine (0.052 mL, 0.647 mmol) and piperidine (0.213 mL, 2.16 mmol) in 5 mL of DCE. The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 52 mg (20%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.52 - 1.58 (m, 2 H), 1.59 - 1.68 (m, 2 H), 1.70 (s, 9 H), 1.73 - 1.84 (m, 3 H), 1.88 - 1.97 (m, 2 H), 2.34 - 2.42 (m, 1 H), 2.98 (t, J=11.72 Hz, 2 H) 3.35 (td, J=11.57, 2.44 Hz, 2 H) 3.45 (s, 3 H) 3.50 - 3.53 (m, 2 H), 3.54 - 3.59 (m, 2 H), 3.68 - 3.74 (m, 2 H), 3.93 (d, J=3.12 Hz, 1 H), 3.96 (d, J=2.15 Hz, 1 H), 4.56 (d, J=7.42 Hz, 2 H), 7.71 (dd, J=8.98, 2.15 Hz, 1 H), 7.89 (d, J=1.76 Hz, 1 H), 8.00 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 477.0; Anal. Calcd for C₂₅H₄₀N₄O₃S + 3.4 TFA + 0.9 H₂O: C, 43.38; H, 5.17; N, 6.36. Found: C, 43.41; H, 5.14; N, 6.36.

Example 8

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-2-methoxy-*N*-methylethanesulfonamide**

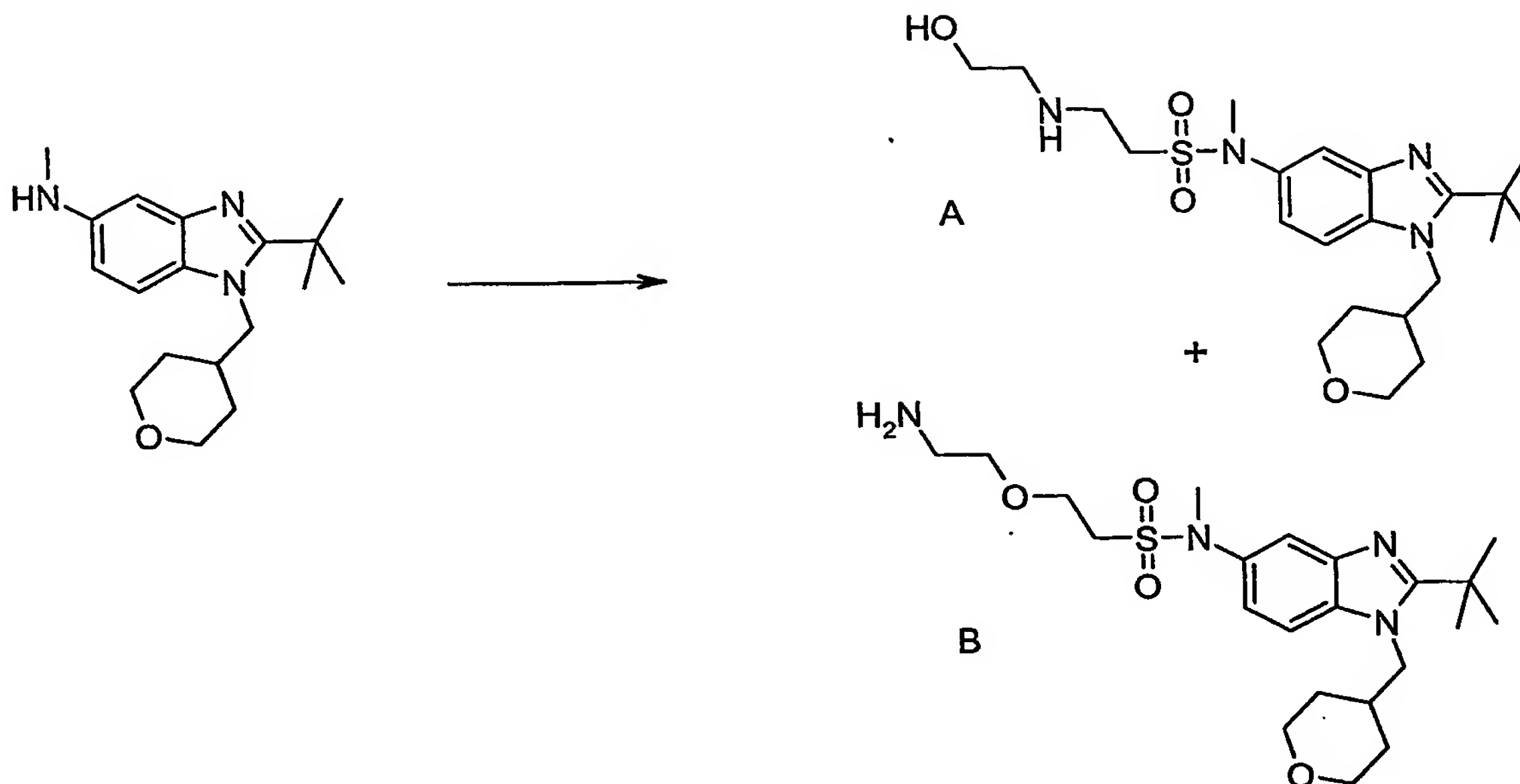


- 5 Following the same procedure as in Example 5 using 2-*tert*-butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (60 mg, 0.199 mmol), 2-chloro-1-ethanesulfonyl chloride (0.024 mL, 0.299 mmol), pyridine (0.024 mL, 0.299 mmol) and 2M NaOMe/MeOH (0.5 mL) in 3 mL of DCE. The solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous
- 10 NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 20 mg (20%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.52 - 1.57 (m, 2 H), 1.57 - 1.63 (m, 2 H), 1.67 (s, 9 H), 2.35 - 2.41 (m, 1 H), 3.32 - 3.35 (m, 4 H), 3.36 (s, 3 H), 3.38 (s, 3 H), 3.75 (t, J=5.57
- 15 Hz, 2 H), 3.93 (d, J=3.51 Hz, 1 H), 3.95 (d, J=3.71 Hz, 1 H), 4.52 (d, J=7.62 Hz, 2 H), 7.66 (dd, J=8.98, 2.15 Hz, 1 H), 7.83 (d, J=1.95 Hz, 1 H), 7.92 (d, J=9.18 Hz, 1 H); MS (ESI) (M+H)⁺ 424.0; Anal. Calcd for C₂₁H₃₃N₃O₄S + 1.2 TFA + 0.9 H₂O: C, 48.74; H, 6.29; N, 7.29. Found: C, 48.69; H, 6.19; N, 7.50.

20 **Example 9**

Product A: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-2-[(2-hydroxyethyl)amino]-*N*-methylethanesulfonamide

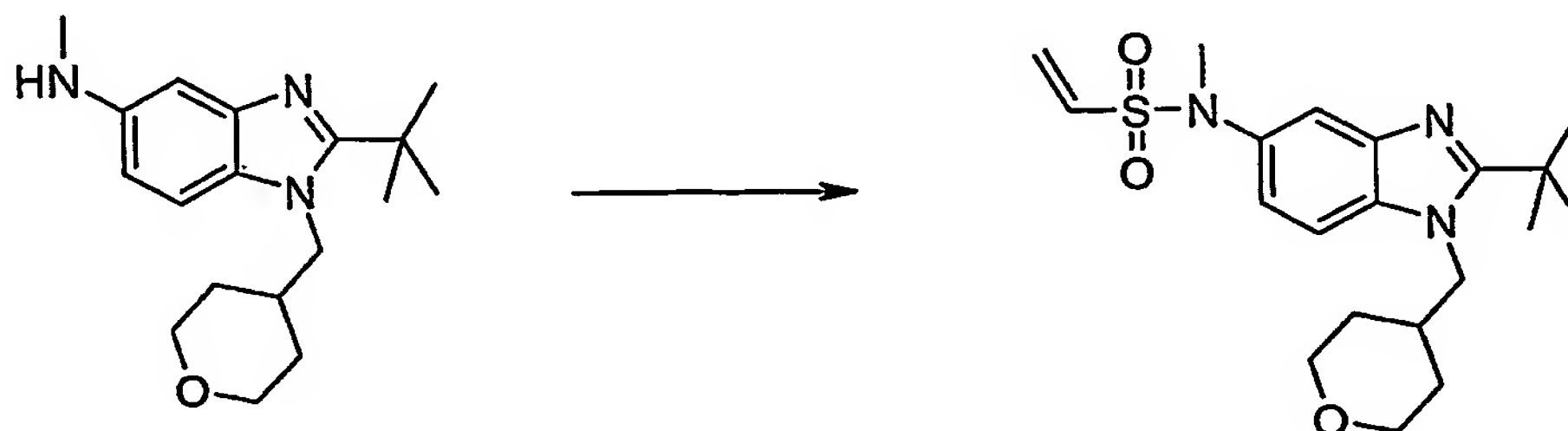
Product B: 2-(2-Aminoethoxy)-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylethanesulfonamide



Following the same procedure as in Example 5 using 2-tert-butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (33 mg, 0.109 mmol), 2-chloro-1-ethanesulfonyl chloride (0.014 mL, 0.131 mmol), pyridine (0.013 mL, 0.164 mmol) and ethanolamine (0.066 mL, 1.09 mmol) in 3 mL of DCE. The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O and lyophilized affording the title compounds as the corresponding TFA salts. Yield: Product A: 37 mg (60%); Product B: 14 mg (23%). Product A: ¹H NMR (400 MHz, METHANOL-D₄): δ 1.51 - 1.57 (m, 2 H), 1.56 - 1.63 (m, 2 H), 1.68 (s, 9 H), 2.33 - 2.42 (m, 1 H), 3.16 - 3.21 (m, 2 H), 3.35 (td, J=11.57, 2.44 Hz, 2 H), 3.45 (s, 3 H), 3.49 - 3.55 (m, 2 H), 3.59 - 3.64 (m, 2 H), 3.75 - 3.80 (m, 2 H), 3.93 (d, J=3.12 Hz, 1 H), 3.96 (d, J=2.73 Hz, 1 H), 4.54 (d, J=7.62 Hz, 2 H), 7.68 (dd, J=8.98, 1.95 Hz, 1 H), 7.85 (d, J=1.56 Hz, 1 H), 7.97 (d, J=8.79 Hz, 1 H); MS (ESI) (M+H)⁺ 453.0; Anal. Calcd for C₂₂H₃₆N₄O₄S + 2.6 TFA + 1.5 H₂O: C, 42.10; H, 5.40; N, 7.22. Found: C, 42.02; H, 5.25; N, 7.41. Product B: ¹H NMR (400 MHz, METHANOL-D₄): δ 1.50 - 1.56 (m, 2 H), 1.55 - 1.64 (m, 2 H), 1.66 (s, 9 H), 2.33 - 2.41 (m, 1 H), 3.07 (s, 3 H), 3.18 (t, J=5.66 Hz, 2 H), 3.31 - 3.40 (m, 4 H), 3.62 (t, J=5.57 Hz, 2 H), 3.90 - 3.97 (m, 4 H), 4.47 (d, J=7.62 Hz, 2 H), 6.90 (d, J=2.34 Hz, 1 H), 7.16 (dd, J=9.37, 2.34 Hz, 1 H), 7.75 (d, J=9.37 Hz, 1 H); MS (ESI) (M+H)⁺ 453.0; Anal. Calcd for C₂₂H₃₆N₄O₄S + 1.5 TFA: C, 48.15; H, 6.06; N, 8.97. Found: C, 48.34; H, 6.22; N, 8.57.

Example 10

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylethanesulfonamide**

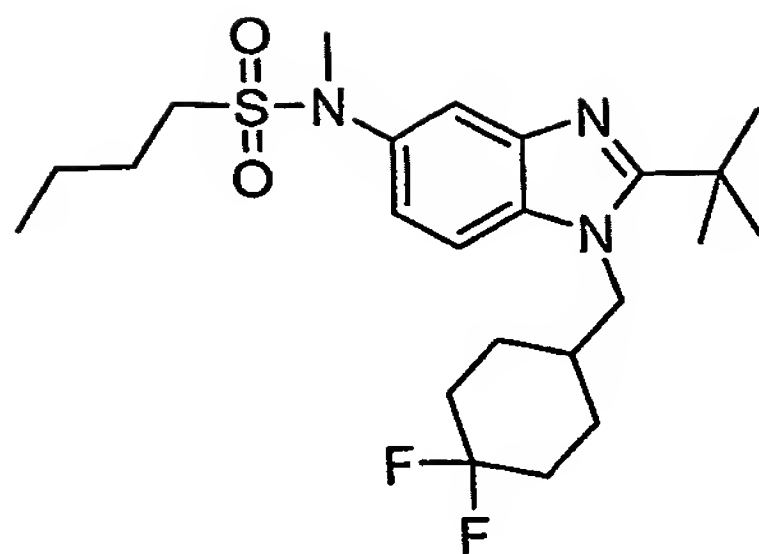


- 5 Following the same procedure as in Example 5 using 2-*tert*-butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (49 mg, 0.163 mmol), 2-chloro-1-ethanesulfonyl chloride (0.022 mL, 0.212 mmol), pyridine (0.020 mL, 0.245 mmol) and 2M ammonia/EtOH (0.5 mL) in 3 mL of DCE. The solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous
- 10 NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 10-60% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 34 mg (41%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.52 - 1.58 (m, 2 H), 1.58 - 1.67 (m, 2 H), 1.69 (s, 9 H), 2.34 - 2.43 (m, 1 H), 3.32 (s, 3 H), 3.33 - 3.39 (m, 2 H), 3.93 (d, J=3.12 Hz, 1 H), 3.95
- 15 (d, J=3.52 Hz, 1 H), 4.55 (d, J=7.42 Hz, 2 H), 6.10 (d, J=8.79 Hz, 1 H), 6.13 (d, J=2.15 Hz, 1 H), 6.70 (dd, J=16.50, 10.06 Hz, 1 H), 7.61 (dd, J=8.98, 2.15 Hz, 1 H), 7.76 (d, J=1.56 Hz, 1 H), 7.96 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 392.0; Anal. Calcd for C₂₀H₂₉N₃O₃S + 1.3 TFA + 0.3 H₂O: C, 49.79; H, 5.71; N, 7.71. Found: C, 49.81; H, 5.77; N, 7.74.

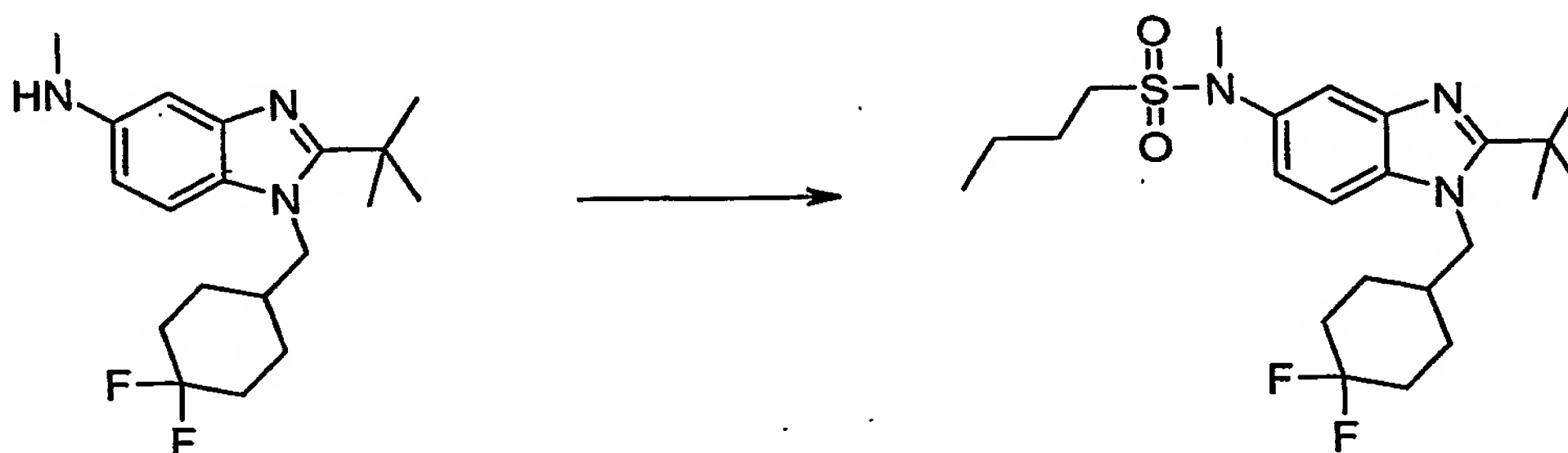
20

Example 11

***N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylbutane-1-sulfonamide**

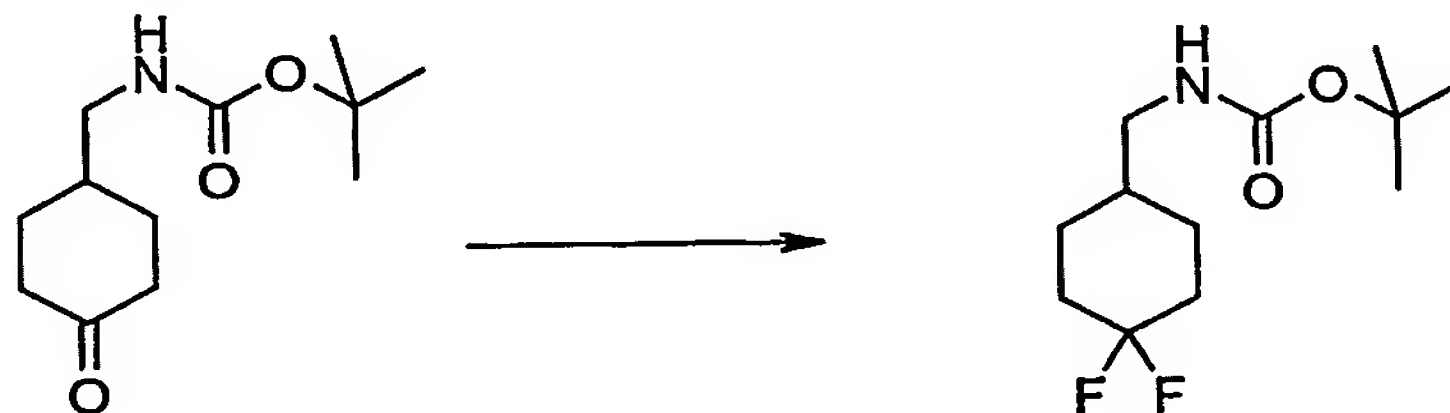


Step A: *N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylbutane-1-sulfonamide



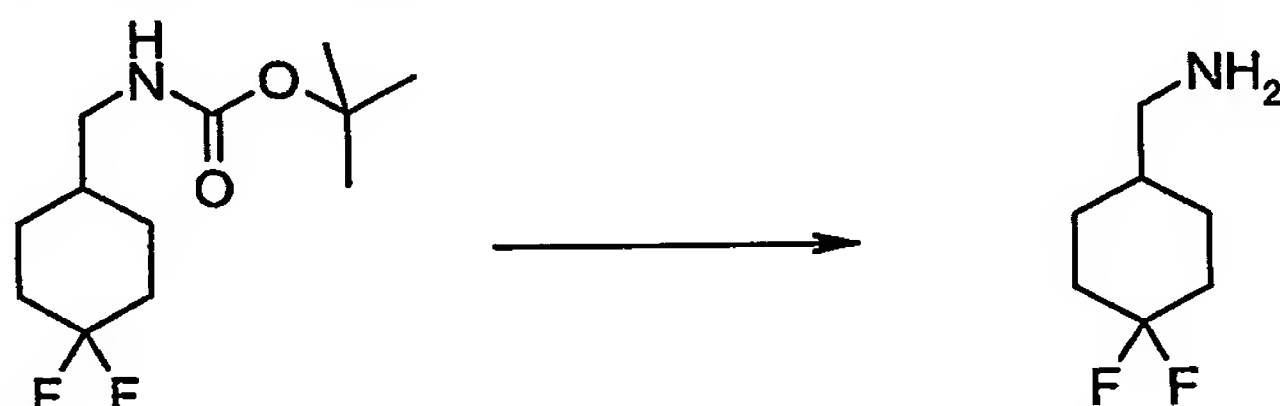
- 5 2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine (for preparation see following Steps B, C, D, E, F and G) (46 mg, 0.137 mmol) and 1-butan-1-ylsulfonyl chloride (0.063 mL, 0.411 mmol) were stirred in 3 mL of DCM containing a catalytic amount of DMAP at rt for 6h. The solvent was evaporated and the product was purified by reversed-phase HPLC using 10-75% CH₃CN/H₂O and
- 10 lyophilized affording the title compound as the corresponding TFA salt. Yield: 48 mg (62%). ¹H NMR (400 MHz, METHANOL-D₄): δ 0.92 (t, J=7.32 Hz, 3 H), 1.43 (td, J=14.94, 7.42 Hz, 2 H), 1.52 - 1.63 (m, 2 H), 1.69 (s, 9 H), 1.70 - 1.76 (m, 4 H), 1.76 - 1.84 (m, 2 H), 2.02 - 2.12 (m, 2 H), 2.22 - 2.31 (m, 1 H), 3.10 - 3.17 (m, 2 H), 3.41 (s, 3 H), 4.56 (d, J=7.62 Hz, 2 H), 7.69 (dd, J=8.98, 2.15 Hz, 1 H), 7.82 (d, J=1.76 Hz, 1 H), 7.96 (d, J=9.18 Hz, 1 H); MS (ESI) (M+H)⁺ 456.
- 15

Step B: *tert*-Butyl [(4,4-difluorocyclohexyl)methyl]carbamate



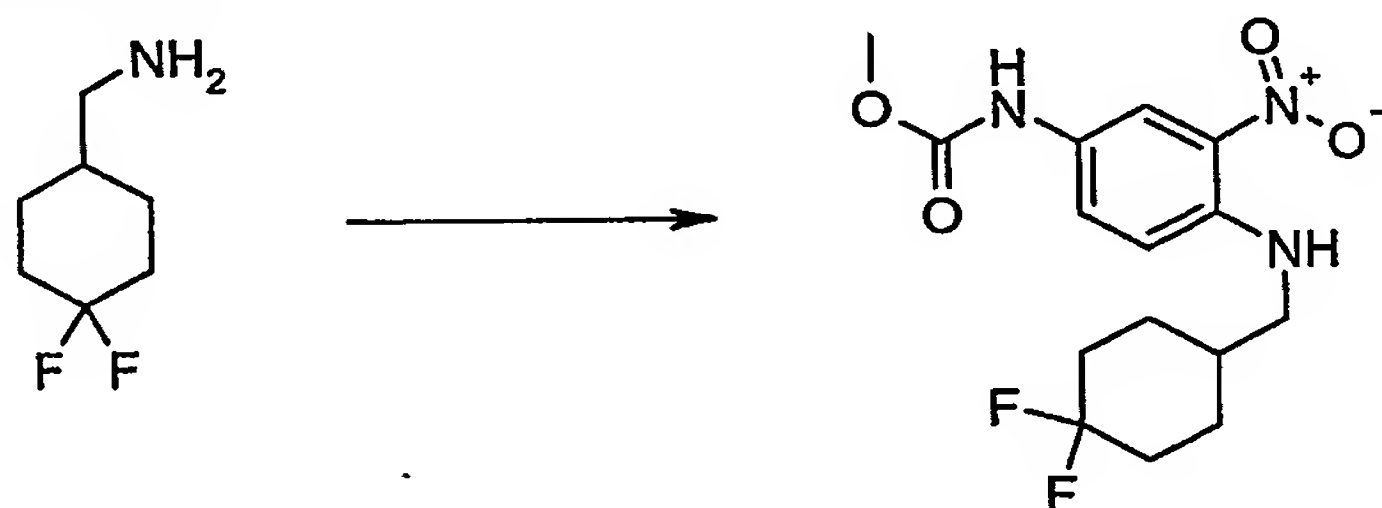
4-N-Boc-aminomethyl cyclohexanone (1.00g, 4.4 mmol) was dissolved in 30 mL of DCM at 0°C. DAST (1.45 mL, 11.0 mmol) was added dropwise and the solution was stirred at rt overnight. The solution was washed with aqueous 5% KHSO₄ solution, saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 3:1 / hexanes : EtOAc as eluent. Yield: 508mg (46%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.19 - 1.36 (m, 2 H), 1.44 (s, 9 H), 1.51 - 1.56 (m, 1 H), 1.59 - 1.75 (m, 2 H), 1.75 - 1.84 (m, 2 H), 2.01 - 2.16 (m, 2 H), 3.03 (t, *J*=6.54 Hz, 2 H), 4.62 (br.s, 1 H).

10 **Step C: [(4,4-Difluorocyclohexyl)methyl]amine hydrochloride**



tert-Butyl [(4,4-difluorocyclohexyl)methyl]carbamate (505 mg, 2.03 mmol) was stirred in 5 mL of 1M HCl/AcOH at rt for 2h. The solvent was evaporated. The residue was washed with ether, filtered and dried. Yield: 330 mg (88%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.28 - 1.40 (m, 2 H), 1.71 - 1.82 (m, 2 H), 1.84 (d, *J*=3.12 Hz, 2 H), 1.86 - 1.89 (m, 1 H), 2.03 - 2.15 (m, 2 H), 2.85 (d, *J*=7.03 Hz, 2 H).

Step D: Methyl (4-[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)carbamate



20

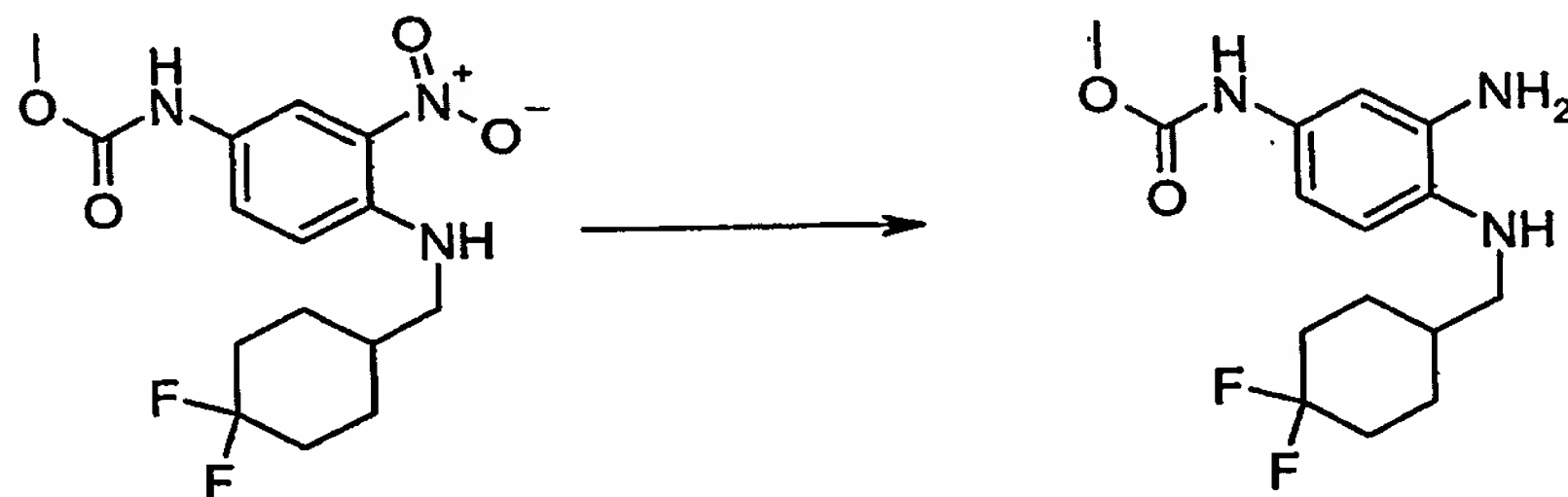
Following the same procedure as in Step C of Example 4 using [(4,4-difluorocyclohexyl)methyl]amine hydrochloride (210 mg, 1.12 mmol), methyl (4-fluoro-3-nitrophenyl)carbamate (200 mg, 0.934 mmol) and TEA (0.390 mL, 2.80 mmol) in 10 mL of EtOH. The crude product was purified by silica gel flash chromatography using 5% ether/DCM as eluent. Yield: 200 mg (62%). ¹H NMR

25

(400 MHz, CHLOROFORM-D): δ 1.34 - 1.47 (m, 2 H), 1.65 - 1.75 (m, 2 H), 1.78 - 1.85 (m, 1 H), 1.90 - 1.93 (m, 1 H), 1.94 - 1.97 (m, 1 H), 2.10 - 2.21 (m, 2 H), 3.23 (dd, $J=6.64, 5.66$ Hz, 2 H), 3.78 (s, 3 H), 6.48 (br.s, 1 H), 6.83 (d, $J=9.18$ Hz, 1 H), 7.66 (br.s, 1 H), 8.05 (br.s, 1 H), 8.07 (d, $J=2.54$ Hz, 1 H).

5

Step E: Methyl (3-amino-4-[(4,4-difluorocyclohexyl)methyl]amino}phenyl)carbamate

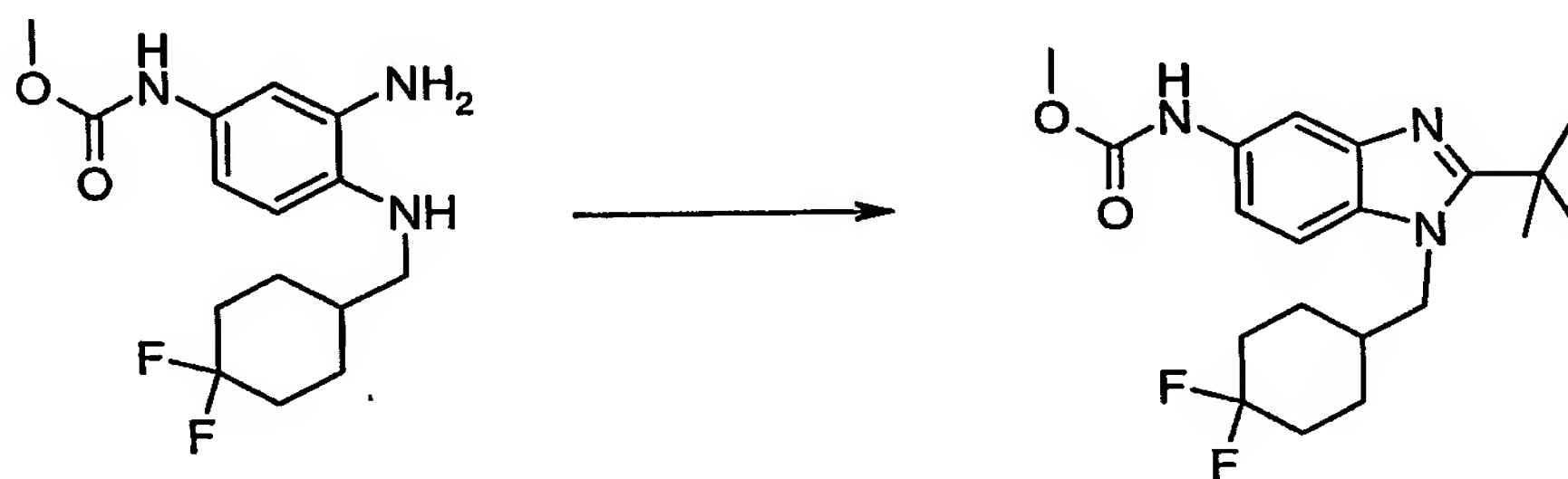


Following the same procedure as in Step D of Example 4 using methyl (4-[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)carbamate (200 mg, 0.583 mmol) and a catalytic amount of 10% Pd/C in 20 mL of EtOAc. Yield: 185 mg (99%). MS (ESI) (M+H)⁺ 314.29.

10

Step F: Methyl {2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}carbamate

15

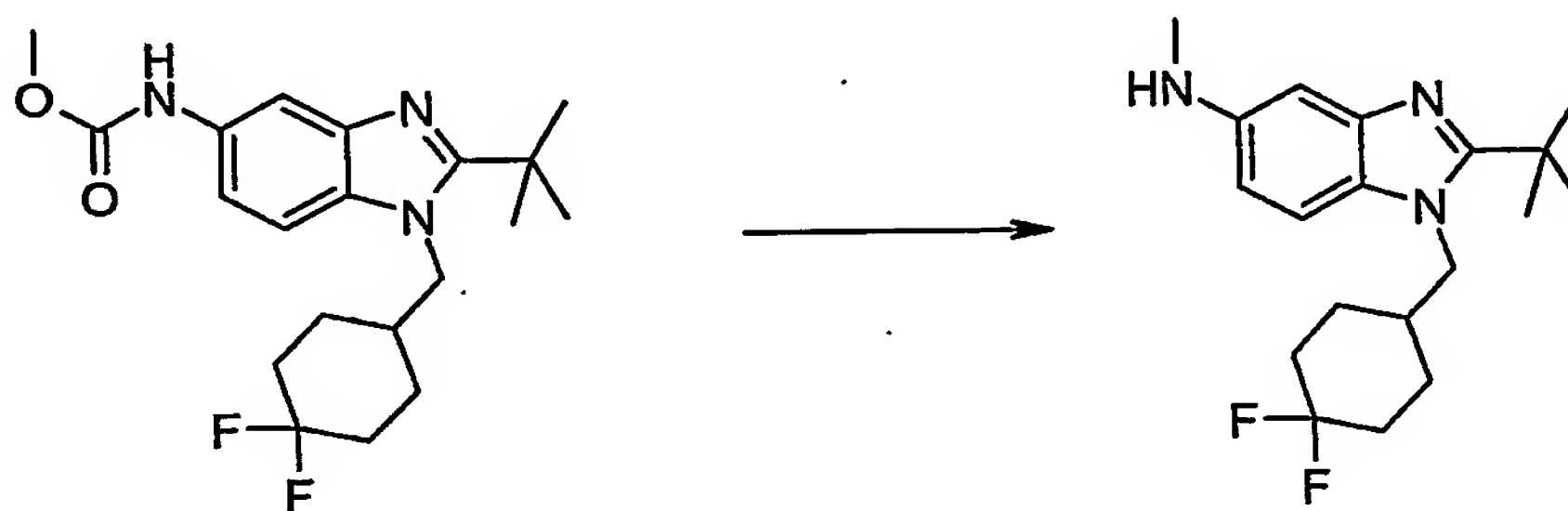


Methyl (3-amino-4-[(4,4-difluorocyclohexyl)methyl]amino}phenyl)carbamate (185 mg, 0.590 mmol) and DMAP (15 mg, 0.118 mmol) were dissolved in 10 mL of DCM. Trimethylacetyl chloride (0.080 mL, 0.649 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The solvent was concentrated. The residue was dissolved in 4 mL of DCE and P₂O₅ (catalytic) was added and the solution was heated at 125°C for 1h using a Personal Chemistry microwave apparatus.

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The solution was washed with aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The crude product was purified by silica gel flash chromatography using 50 to 75% EtOAc / hexanes. Yield: 122 mg (54%); ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.43 - 1.52 (m, 2 H), 1.55 (s, 9 H), 1.57 - 1.66 (m, 2 H), 1.67 - 1.74 (m, 2 H), 2.08 - 2.18 (m, 3 H), 3.79 (s, 3 H), 4.19 (d, *J*=7.42 Hz, 2 H), 6.63 (br.s, 1 H), 7.23 (d, *J*=8.79 Hz, 1 H), 7.37 - 7.46 (m, 1 H), 7.62 (d, *J*=1.76 Hz, 1 H).

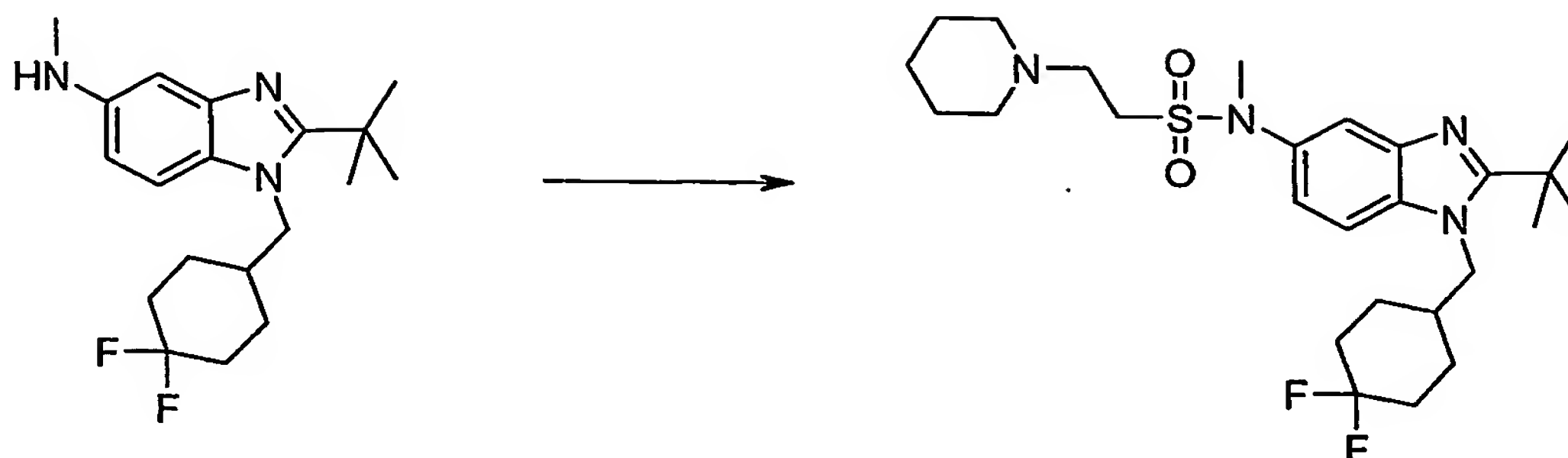
Step G: 2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine



Methyl {2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}carbamate (115 mg, 0.303 mmol) was dissolved in 10 mL of THF at 0°C. 1M HCl/ether (0.425 mL, 0.424 mmol) was added and the solution was stirred at 0°C for 15 min. LiAlH₄ (57 mg, 1.52 mmol) was added slowly and the solution was stirred at rt overnight. The reaction was quenched at 0°C by the addition of MeOH (1 mL) and water (2 mL). Anhydrous Na₂SO₄ (5.0 g) was added and the solution was stirred at rt for 30 min. The solution was filtered and the solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. Yield: 95 mg (93%). ¹H NMR (400 MHz, CHLOROFORM-D): δ 1.41 - 1.51 (m, 2 H), 1.54 (s, 9 H), 1.57 - 1.67 (m, 2 H), 1.68 - 1.76 (m, 3 H), 2.07 - 2.17 (m, 3 H), 2.87 (s, 3 H), 4.15 (d, *J*=7.42 Hz, 2 H), 6.61 (dd, *J*=8.59, 2.34 Hz, 1 H), 7.01 (d, *J*=1.95 Hz, 1 H), 7.09 (d, *J*=8.59 Hz, 1 H).

Example 12

***N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-2-piperidin-1-ylethanesulfonamide**



- 2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine (45 mg, 0.134 mmol) and pyridine (0.022 mL, 0.268 mmol) were dissolved in 3 mL of DCE. 2-Chloro-1-ethanesulfonyl chloride (0.021 mL, 0.201 mmol) was added and the solution was stirred at rt for 2h. Piperidine (0.066 mL, 0.670 mmol) was added and the solution was stirred at 75°C for 2h. The solution was washed with saturated aqueous NaHCO₃ solution, brine and dried over anhydrous MgSO₄. The product was purified by reversed-phase HPLC using 10-50% CH₃CN/H₂O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 40 mg (48%). ¹H NMR (400 MHz, METHANOL-D₄): δ 1.53 - 1.63 (m, 3 H), 1.68 (s, 9 H), 1.71 - 1.77 (m, 4 H), 1.77 - 1.85 (m, 3 H), 1.90 - 1.97 (m, 2 H), 2.03 - 2.12 (m, 2 H), 2.20 - 2.30 (m, 1 H), 2.94 - 3.04 (m, 2 H), 3.45 (s, 3 H), 3.51 - 3.59 (m, 4 H), 3.67 - 3.73 (m, 2 H), 4.55 (d, J=7.62 Hz, 2 H), 7.68 (dd, J=8.98, 2.15 Hz, 1 H), 7.86 (d, J=1.95 Hz, 1 H), 7.95 (d, J=8.98 Hz, 1 H); MS (ESI) (M+H)⁺ 511.0; Anal. Calcd for C₂₅H₄₀N₄O₂SF₂ + 2.7 TFA + 1.0 H₂O: C, 45.08; H, 5.39; N, 6.70. Found: C, 45.01; H, 5.32; N, 7.00.